



Seminars in

October 2019

FETAL & NEONATAL

medicine

**CHRONIC VENTILATOR
DEPENDENCE IN INFANTS**



collected by Ahmed Manfy

Seminars in Fetal & Neonatal Medicine

Amsterdam • Boston • London • New York • Oxford • Paris • Philadelphia • San Diego • St. Louis

Editorial Board

Editor-in-Chief

Steven Donn

*University of Michigan Health System
Ann Arbor, USA*

Associate Editors

R Agarwal, *All India Institute of Medical Sciences,
New Delhi, India*

M Blennow, *Karolinska Institutet*, Stockholm, Sweden*

K Boggess, *University of North Carolina School of Medicine,
Chapel Hill, USA*

E Boyle, *University of Leicester Department of Health Sciences,
Leicester, UK*

F Chervenak, *Weill Cornell Medical College, New York, USA*

L Cornette, *Az Sint-Jan, Brugge, Belgium*

B A Darlow, *Christchurch School of Medicine, Christchurch,
New Zealand*

P G Davis, *Royal Women's Hospital, Melbourne, Australia*

V Fellman, *Lund University, Lund, Sweden*

N Finer, *University of California at San Diego (UCSD), San Diego, USA*

A van Kaam, *Emma Children's Hospital, Amsterdam, Netherlands*

G Lista, *Milano, Italy*

Former Editor-in-Chief

M I Levene

*University of Leeds,
Leeds, UK*

K Maršál, *Lund University, Lund, Sweden*

P C Ng, *Chinese University of Hong Kong, New Territories,
Hong Kong*

D Peebles, *University College London (UCL)*, London, UK*

J M Perlman, *Weill Cornell Medical College, New York, USA*

C Poets, *Tuebingen University Hospital, Tuebingen,
Germany*

E Saliba, *University of Tours, Tours, France*

S Sinha, *James Cook University Hospital, Middlesbrough,
UK*

N E Vain, *Fundación para la Salud Materno Infantil
(FUNDASAMIN), Buenos Aires, Argentina*

M Vento, *University of Valencia, Valencia, Spain*

L de Vries, *Wilhelmina Children's Hospital, UMC, Utrecht,
Netherlands*



Editorial

Chronic ventilator dependence in infants



The first reference to positive pressure ventilation and tracheostomies was published by Andreas Vesalius in 1543. An excerpt from his treatise on anatomy entitled *De Humani Corporis Fabrica* states, “But that life may be restored to the animal, an opening must be attempted in the trunk of the trachea, into which a tube of reed or cane should be put; you will then blow into this, so that the lung may rise again and take air” [1]. Over the next several centuries, experiments were being performed to better understand the relationship between the lungs and circulation, but it wasn't until the late 19th century where the prototype for the first negative pressure ventilator was built. This became the basis of the widely used iron lung that was developed in Boston by Drinker and Shaw in 1929 and used to treat patients during the polio epidemic. There were many disadvantages of the iron lung. It was large and bulky which limited portability and access to the patient. During this time, Bjorn Ibsen, an anesthesiologist from Boston, recommended tracheostomy and positive pressure ventilation via “hand bagging” as there were no positive pressure ventilators available at the time. By the end of the epidemic, approximately 1,500 students provided manual ventilation for a total of 165,000 hours [2]. To better care for those requiring chronic mechanical ventilation, the establishment of intensive care units were created. The discrepancy between the increasing number of pediatric patients requiring long-term ventilation and the number of available pediatric ICU beds prompted the need for families to manage these patients at home.

Since its advent in 1977, the LP3 portable volume ventilator made home use of positive pressure devices a possibility. For the pediatric patient, home mechanical ventilation reduces hospital costs, improves quality of life, enhances development, and reduces exposure to infectious diseases [3,4]. The benefits of home care are obvious, but the decision to shift care from a PICU to a home setting can be a complicated one. The technology dependent child belongs to a heterogeneous group of patients whose underlying pathology can be attributed to neuromuscular disease, severe prematurity resulting in bronchopulmonary dysplasia (BPD), or defective respiratory drives. Despite these variations in etiology, the majority have similar medical and social needs that need to be considered in order to successfully and safely provide care for these patients at home. In 2016, The Pediatric Assembly of the American Thoracic Society (ATS) developed evidence-based clinical practice guidelines for management of children requiring invasive mechanical ventilation at home. These guidelines established recommendations addressing coordination of care, readiness for home

care, training of caregivers, and necessary equipment [5].

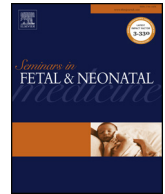
In this issue of *Seminars of Fetal & Neonatal Medicine*, we review best practices for mechanical ventilation of infants with tracheostomy-dependent chronic respiratory failure. Dr. Zhang et al., describe differences in ventilation strategies between neonatal respiratory distress syndrome and established chronic lung disease. Dr. Bhombal explains the complex cardiopulmonary interactions in mechanically ventilated infants. Dr. Flannagan's and Dr. Healy's article covers indications and timing for both tracheostomy placement and decannulation. Drs. Fierro and Panitch discuss the process of transitioning from hospital ventilators to portable home ventilators. Dr. Benscoter and colleagues review steps necessary to prepare families to care for their mechanically ventilated infants in the home. Following successful transition to home, Chou and Webster highlight advances in telemedicine for technology-dependent children. Finally, Drs. Koltsida and Konstantinopoulou provide an update on long-term outcomes in children requiring long-term mechanical ventilation for chronic lung disease. Taken together, these articles provide a thorough summary of the technological progress in the care of infants with chronic respiratory failure from neonatal intensive care unit to the home care setting.

References

- [1] Vesalius ADe humani corporis fabrica. 1543.
- [2] Sykes MK, Bunker JP. The anaesthetist and the fever hospital. In: Sykes MK, Bunker JP, editors. *Anaesthesia and the practice of medicine: historical perspectives*. London: The Royal Society of Medicine Press Ltd; 2007. p. 161–71.
- [3] Marchese S, Coco DL, Coco AL. Outcome and attitudes toward home tracheostomy ventilation of consecutive patients: a 10-year experience. *Respir Med* 2008;102(3):430–6.
- [4] Downes JJ, Boroughs DS, Dougherty J, Parrru M. A statewide program for home care of children with chronic respiratory failure. *Caring* 2007;26(9):16–8.
- [5] Sterni LM, Collaco JM, Baker CD, Carroll JL, Sharma GD, Brozek JL, et al. ATS Pediatric Chronic Home Ventilation Workgroup. An official American thoracic society clinical practice guideline: pediatric chronic home invasive ventilation. *Am J Respir Crit Care Med* 2016 Apr;193(8):e16–35.

Joseph Piccione (D.O., M.S.)*, Alexiou Stamatia (M.D)
 Division of Pulmonary Medicine, Children's Hospital of Philadelphia,
 University of Pennsylvania School of Medicine, Philadelphia, PA, USA
 E-mail addresses: piccionej@email.chop.edu (J. Piccione),
AlexiouS1@email.chop.edu (A. Stamatia).

* Corresponding author.



Ventilation strategies in transition from neonatal respiratory distress to chronic lung disease

Yi Sun^b, Huayan Zhang^{a,b,*}

^a Newborn and Infant Chronic Lung Disease Program, Division of Neonatology, Children's Hospital of Philadelphia and University of Pennsylvania Perelman School of Medicine, 3615 Civic Center Blvd, Philadelphia, PA 19104, USA

^b Division of Neonatology and Center for Newborn Care, Guangzhou Women and Children's Medical Center, No.9 Jin Sui Road, Zhujiang New City, Guangzhou 510623, Guangdong Province, PR China

ABSTRACT

Despite the advance in neonatal care over the past few decades, preventing preterm infants with respiratory distress syndrome progress to bronchopulmonary dysplasia remained challenging. In this review, we will discuss the respiratory support strategies in preterm infants with RDS evolving into BPD based on the changes in pulmonary mechanics and pathophysiology as well as currently available evidence.

1. Introduction

The advance in neonatal intensive care has enabled the survival of very premature infants with extremely low birth weight. However, bronchopulmonary dysplasia (BPD) remained as one of the most common complications leading to both short and longer term mortality and morbidities. Survivors of BPD often face chronic cardiopulmonary impairment, growth failure, and poor neurodevelopmental outcomes, which brings a major burden to the babies, their families, the health care system and the society. Prevention of BPD has therefore been the focus of research for the recent years. However, most of the studies concentrated on the first few days of life and few have examined the factors that may affect the transition from early respiratory insufficiency due to respiratory distress syndrome (RDS) to established BPD, and the best strategies to support a preterm infant in this stage to prevent the advance to BPD.

This review attempts to summarize the current available evidence that focuses on the respiratory support strategies to support infants in transition from RDS to BPD. Although other managements such as medication use, PDA management and others are also important in preventing BPD, they are beyond the scope of this review.

2. Changes in pathophysiologic and pulmonary mechanics from RDS to BPD

Both RDS and BPD can be considered developmental diseases that start off with infants born prematurely in the late canalicular or

saccular phases of lung development. Multiple characteristics of the premature respiratory system contribute to the pathophysiology and clinical presentation of RDS (Fig. 1). Of these, the developmental deficiency of surfactant is the most important, which contributes to not only the pathological findings of RDS but also to the decrease host defense mechanisms in preterm infants. All four components of surfactant proteins are developmentally and hormonally regulated and increase markedly in the first few days after preterm birth [1,2]. However, their levels can be modulated by the pathogens, toxins and reactive oxygen species in the local microenvironment [3]. In addition to surfactant deficiency, all the other factors that contribute to the pathophysiology of RDS can also increase the preterm infant's susceptibility to injury and poor lung growth. Therefore maintaining a healthy local microenvironment would have critical importance for preterm infants to improve from RDS and enter into a phase of injury repair and healthy lung growth to prevent the progression to BPD.

Unfortunately, this healthy microenvironment is hard to establish or maintain for some of the infants. A variety of prenatal and post-natal factors will influence postnatal lung growth and contribute to lung injury. Genetic and prenatal factors set the stage for increased susceptibility to inflammation and growth failure. Postnatal factors directly or indirectly result in lung injury and poor growth and repair. As a result, pathophysiology of BPD in the current era is characterized by an arrest or delay in alveolar/pulmonary vascular development and various degrees of lung injury. However, depending on the status of lung development at the time of postnatal insults and the interaction between the predisposed susceptibility and the injury, infants with BPD will have

* Corresponding author. Newborn and Infant Chronic Lung Disease Program, Division of Neonatology, Children's Hospital of Philadelphia and University of Pennsylvania Perelman School of Medicine, 3615 Civic Center Blvd, Philadelphia, PA 19104, USA.

E-mail addresses: ysunbella@163.com (Y. Sun), zhangh@email.chop.edu (H. Zhang).

<https://doi.org/10.1016/j.siny.2019.101035>

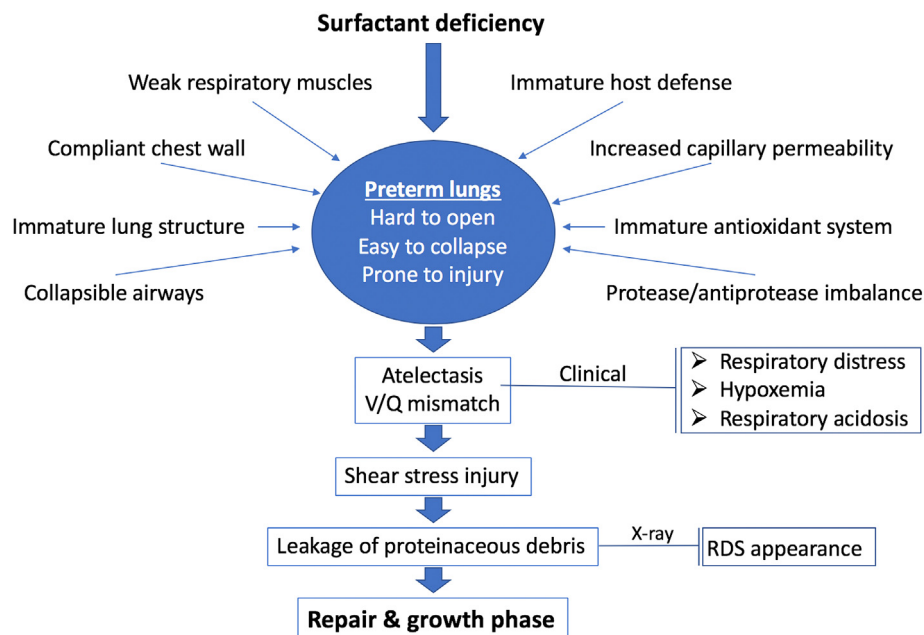


Fig. 1. Characteristics of the premature respiratory system contribute to the pathophysiology and clinical presentation of RDS.

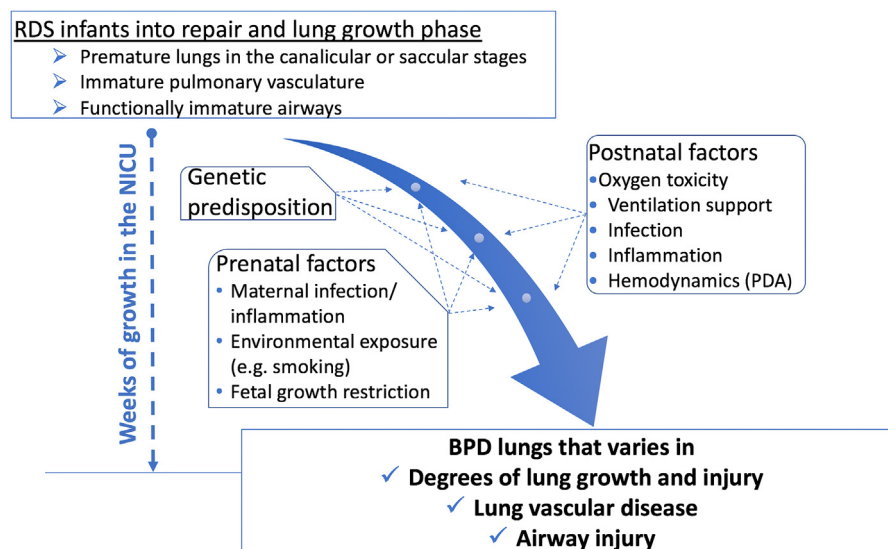


Fig. 2. Interactions of pre-postnatal factors and lung developmental stages resulting in variations in BPD pathophysiology.

variation in the degrees of lung parenchymal disease, pulmonary vascular disease and airway problems (Fig. 2).

The pulmonary mechanics of an infant with RDS is characterized by stiff lungs, i.e. hard to open and easy to collapse, due to decreased lung compliance and high elastance. Without anatomical obstruction, the airway resistance is usually normal in these infants and hence the time constant (the product of compliance times resistance) is usually short, which means that the alveoli of these infant are fast to inflate and deflate. The lung mechanics of a BPD infant, however, is hard to determine as ventilation in these lungs is often uneven with areas of atelectasis and areas of hyperinflation or cystic changes. Therefore, the lung compliance may be high in some areas but low in others. The airway resistance is often high due to hyperplasia of the airway smooth muscles, air trapping, airway malacia or secretions. In these lungs with heterogenous ventilation, some parts of the lung has very long time constant and therefore require much longer time inspiration time to inflate and longer expiration time to deflate [4].

3. Respiratory support strategies to prevent BPD

3.1. Goals of respiratory support

Since lung injury plays an important role in the development of BPD, much of research efforts has focused on finding proper respiratory support strategies that avoid or minimize lung injury. However, we need to keep in our minds that the ultimate goal of respiratory support is to promote healthy life, and avoiding lung injury is only one aspect helping to reach this goal. It is important to remember we are trying to support a whole person, not just a pair of lungs as the lung health will affect the well-being of the other organ systems and vice versa. Take nutritional status and the development of BPD for example, poor nutrition will lead to difficulties with proper lung development, which is the key aspect of pathogenesis of BPD. Meanwhile, chronic respiratory insufficiency in infants with evolving or established BPD will also create challenges for the infant to grow properly (Fig. 3). Therefore the goal of respiratory support for a preterm infant transitioning from RDS to BPD

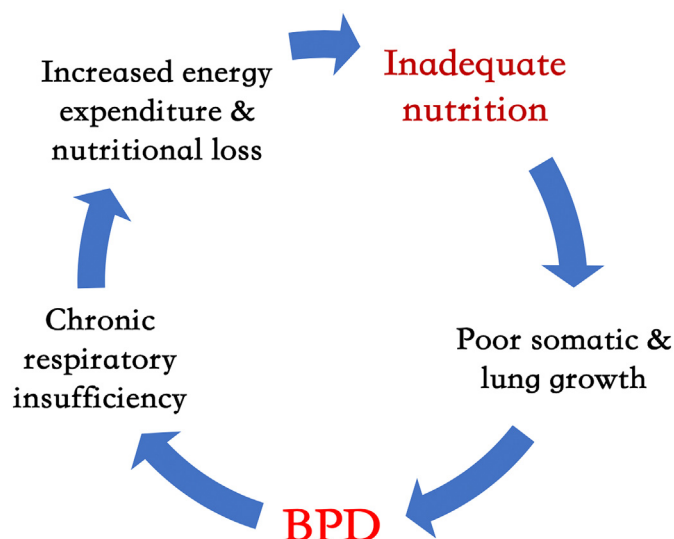


Fig. 3. Interaction of nutrition and BPD.

should not be aimed solely at keeping PCO_2 and SPO_2 in acceptable ranges, but rather providing adequate but not too much support that will adequately support proper growth and injury repair while avoiding or minimizing further lung injury.

The concept of lung protective ventilation has been introduced in an attempt to minimize lung injury. The main goals of lung protective ventilation strategies are avoiding volutrauma, atelectotrauma and biotrauma (e.g. oxygen toxicity). We will discuss some of the most commonly used approaches in this section.

3.2. Permissive hypercapnia

Permissive hypercapnia is a commonly used lung protective ventilation strategy in the treatment of premature infants. With several studies suggesting the strong association of hypocapnia with poor outcomes in preterm infants, including increased risk of BPD, severe intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and cerebral palsy (CP) [5–8], this approach was quickly and widely adapted worldwide as a method of BPD prevention, before high quality evidence in terms of the efficacy and safety of this approach was available.

The main theoretical benefits of permissive hypercapnia include that through intentional hypoventilation and tolerance of higher pCO_2 levels, we can: 1) Avoid hypocapnia, and its related complications; 2) decrease the level of mechanical ventilation and allow early extubation, thus avoid ventilator associated lung injury; 3) potentially dampen the systemic pro-inflammatory response [9–11] and 4) increased oxygen delivery to tissues and cerebral blood flow preventing cerebral ischemia [12]. Early randomized, controlled trials testing the effect of mild hypercapnia (i.e. $PaCO_2$ 45–55 mmHg as compared to a normocapnia target of 35–45 mmHg), found a trend towards shortened extent of mechanical ventilation and decreased need for ventilator assistance at 36 weeks postmenstrual age (PMA), without increasing adverse neurodevelopmental effects in the mild hypercapnia group [13,14]. However, a meta-analysis of the early trials did not show a significant benefit of permissive hypercapnia in the prevention of death or BPD at 36 weeks [15].

In recent years, data from several randomized trials and observational cohort studies continue to fail to demonstrate the efficacy of this approach in the reduction of BPD but raised more concerns for its safety (Table 1). Furthermore, several other studies provided data demonstrating potential detrimental effects of persistent high pCO_2 levels in a developing preterm infant. Kaiser et al. investigated the effects of pCO_2 levels on cerebral autoregulation and found a progressive loss of

autoregulation with increasing pCO_2 beyond 45 mmHg [16]. Victor et al. studied weekly EEG recordings of 25 babies born between 23 and 32 weeks from 48 h of age till 4 weeks of age. They found that compensated respiratory acidosis may be associated with EEG activity changes in preterm infants over 48 h of age, which may help explain previous finding of reduction in the percentage of active sleep in babies with BPD [17,18]. In a small subset of infants in the PHELIBI trial, infants randomized to high pCO_2 target group was found to have significantly and progressively reduced functional vessel density in the skin suggesting impaired peripheral microcirculation in these infants.

Although permissive hypercapnia is theoretically plausible, the current evidence questions that it is a safe and effective way of reducing the risk of BPD. In addition, most of the trials focused on the effects of mild to moderate hypercapnia (i.e. < 55–60 mmHg) in the first couple of weeks of life. The timing and the range of pCO_2 that may provide benefit, without increasing the adverse outcomes, are not known. We therefore caution the liberal use of permissive hypercapnia to much higher pCO_2 level and well beyond the first weeks of life.

3.3. Non-invasive ventilation

Although mechanical ventilation through endotracheal tubes (ETT) is an effective life-saving therapy for infants with severe respiratory failure, it has been linked to ventilator associated lung injury and increased risk of BPD [19,20]. These injuries can result from over or under-expansion of the lungs leading to mechanical injury from sheer stress and inflammation, or increased risk for infection including ventilator-associated pneumonia and late onset sepsis causing biotrauma [21], and/or free radical damage from oxygen toxicity. Therefore, tremendous efforts have been spent on finding ways to avoid endotracheal intubation (i.e. invasive ventilation) and various modes of non-invasive ventilation have been developed and quickly applied in clinical practice world-wide. Some commonly used modes include nasal continuous positive airway pressure (nCPAP), Bi-level CPAP (BiPAP), nasal intermittent positive pressure ventilation (NIPPV), heated and humidified high flow nasal cannula (HHFNC). In a meta-analysis comparing ventilation strategies with or without ETT in infants < 30 weeks of gestational age, Fischer et al. showed that avoiding the use of a tube had significant benefit in preventing BPD (OR 0.83; 95% CI 0.71–0.96) [22].

nCPAP, providing continuous positive airway pressure through nasal masks or prongs, is the most studied non-invasive method. Data from RCTs has consistently showed a trend towards benefit in early CPAP use and meta-analysis of the trials showed a small but a statistically significant reduction in the risk of death or BPD with a relative risk (RR) of 0.90 (CI 0.83–0.98), and number need to treat to benefit (NNTB) of 25 (CI 13–244) [23]. Early use of CPAP with subsequent selective use of surfactant, is therefore considered an evidence-based strategy to reduce BPD and is endorsed by the American Academy of Pediatrics Committee on Fetus and Newborn [24].

NIPPV has been used as a non-invasive respiratory method for newborns since the 1970s. It combines CPAP with intermittent pressure increases applied through a nasal interface. This intermittent pressure increase may (synchronized NIPPV or sNIPPV) or may not (non-synchronized NIPPV or nsNIPPV) be synchronized with baby's breathing. BiPAP is often included in the NIPPV umbrella. Previous meta-analysis of trials did not provide convincing evidence that NIPPV is advantageous over CPAP as a primary mode of respiratory support, as more than half of the trials found no reduction in the need of intubation [25,26]. When used as a post-extubation support mode, NIPPV may be able to reduce extubation failure, especially when synchronized with patient's breathing and delivered by a ventilator [25,27]. A new meta-analysis by Ekhuagere et al. included more trials since the 2016 and 2017 Cochrane reviews and found that NIPPV was superior to nCPAP in both reducing respiratory failure as the primary support mode after birth (RR 0.55, 95% CI 0.46–0.65; NNT8), and preventing post

Table 1

Recent studies raising concerns of lack of efficacy and potential adverse effects of permissive hypercarbia.

Study	Study group and design	pCO ₂ related observations	Findings and comments
Subramanian 2011	N = 425, BW 500–1499 g, multicenter observational study	pCO ₂ > 50 mmHg in the first 6 days of life compared to normocapnia	Hypercapnia in the first 6 days of life associated with higher incidence of BPD (p = 0.024)
Thome 2015 (PHELBI trial)	N = 359, BW 400–1000 g, GA 23–28 ⁺⁶ weeks, multicenter RCT	3 increasing levels in the first 14 days of life (pCO ₂ high target group 55–65 mmHg vs. control group 40–50 mmHg in the first 3 days of life)	- No difference in death or BPD - Trial was stopped early for no benefit and trend towards benefiting controls - High-target group had lower ventilator pressures but it did not translate into better outcomes - Higher NEC and death in infants with severe disease in the high target group - No difference in NDI/death at 2 year follow up
Ambalvanan 2015	N = 1316, GA 24–27 ⁺⁶ weeks, secondary data analysis of SUPPORT trial	Blood gas in the first 14 days of life	Higher pCO ₂ is an independent predictor of BPD/death, severe IVH/death or NDI/death
Brown 2018	N = 147, GA < 32 weeks, secondary data analysis of a delayed cord clamping trial	Blood gas in the first 72 h of life	- Routine practice of permissive hypercarbia led to low incidence of hypocarbia (2%) but without a significant improvement in BPD or pneumothorax - High mean pCO₂, higher variability of pCO₂ and lower minimum pH were associated with death/severe IVH

extubation failure (RR 0.60, 95% CI 0.45–0.81; NNT 7) [28]. However, despite these beneficial effects, meta-analysis of the trials was not able to show a reduction in BPD with NIPPV, although several small trials suggest synchronized NIPPV may be effective (RR 0.64, 95% CI 0.44–0.95, NNTB 7 (95% CI 4–42) [27]. In recent years, neutrally adjusted ventilatory assist (NAVA) that utilizes the detection of diaphragm electrical activity as the triggering mechanism has been introduced and can be used non-invasively. Some studies have shown that when compared to the traditional NIPPV, non-invasive ventilation NAVA (NIV-NAVA) improves patient-ventilator synchrony during non-invasive nasal ventilation, even in the presence of large air leaks [29]. In a small retrospective study, Lee et al. reported that NIV-NAVA may be promising in reducing extubation failure in preterm infants compared to nCPAP [30]. However, this technique requires a specific ventilator and an expensive esophageal catheter, which hinders the accumulation of high level evidence for its use.

HHHFNC, with its advantages of easy to use, better tolerance and less nasal trauma, has gained popularity as an alternative method of respiratory support to nCPAP or NIPPV. Three meta-analysis published in 2019 compared the effects of HFNC to nCPAP as primary respiratory support or post-extubation support, all concentrating on the need of intubation as the primary outcome [28,31,32]. Their results were not consistent as the studies included in each meta-analysis varied. As primary respiratory support, Ekhuere et al. found that nCPAP is superior to HFNC in preventing respiratory failure, while the other two analysis found no significant difference. When used following extubation, Hong et al. reported nCPAP is associated with fewer extubation failure as compared to HFNC, whereas Fleeman et al. did not and Ekhuere only described that most of the trials did not see difference. Both Hong and Fleeman reported reduced nasal trauma and air leak post extubation with HFNC use. Despite the difference in the reported primary outcomes, all three reports pointed out that few preterm infants born at < 28 weeks' gestation or < 1000 g were included in the analyzed trials and routine use of HFNC in these extremely premature infants is not supported by the current evidence. Manley et al. reported that birth gestational age ≥ 30 weeks and pre-randomization FIO₂ < 0.30 were independent predictors of treatment success in infants randomized to HFNC in their trial [33].

Nasal high frequency ventilation (nHFV), especially in the form of nasal high frequency oscillatory ventilation (nHFOV), is a relatively new mode of non-invasive ventilation but gaining popularity despite scarce evidence. One recently published meta-analysis included 8 small randomized trials with a total of 463 preterm infants, 6 compared nHFOV to nCPAP (359 patients) and 2 compared nHFOV to BiPAP (104 infants) [34]. Sample size of each trial varied from 26 to 126 and most

of infants studied were more than 30 weeks' gestation and over 1500 g at birth. Meta-analysis of these 8 trial data showed that the use of nHFOV was more beneficial in enhancing CO₂ elimination and reduce the risk of intubation. However, the author also reported moderate to high risk of bias in all trials and appropriately pointed out that data from these trial was not sufficient to provide information regarding the appropriate parameter settings of nHFOV, the effect of nHFOV on extremely preterm infants, or the longer term outcomes of nHFOV including risks of BPD, IVH and neurodevelopmental outcomes. In one new single center trial not included in the above meta-analysis, Chen et al. reported that as post extubation support, nHFOV reduced the reintubation rate (OR 0.35, 95% CI 0.18–0.70) and post extubation pCO₂ (MD -7.15, 95% CI -9.95 to -4.80) as compared to nCPAP, especially in infants less than 32 weeks [35]. However, the infants included in this trial were relatively older (30–35 weeks' gestation) and bigger (birth weight 1290–2395 g) and the study was not powered to examine if nHFOV can help reduce BPD. Potential complications found in the trials include nasal trauma and abdominal distention as well as a trend toward higher incidence of NEC in the 32–36 + 6 week group (19.3% vs. 8.6%, p = 0.06). In summary, current data suggests that nHFOV may be effective in preventing intubation. However, the optimal ventilator and ventilator settings, its effects on extremely preterm infants, its role in BPD prevention, as well as its safety profile (including short term effects on IVH and NEC, and long term neurodevelopmental outcomes) will need to be further studies before it can be widely adapted in clinical practice.

3.4. Invasive mechanical ventilation

In the last few decades, mechanical ventilation (MV) has advanced greatly with more sophisticated ventilators that are more suitable for the small newborns. Ventilators in the modern era can provide better synchronization with infants' breathing, compensate for air leak and also with better monitoring capabilities. However, these improvements in the ventilators may not translate into better outcomes of mechanical ventilation unless the clinicians use these tools appropriately. As discussed earlier, the goal of mechanical ventilation is to provide adequate but not too much support. To achieve this goal, the clinician need to have a good understanding of the pulmonary pathophysiology and mechanics, the advantages and disadvantages of different modes of ventilation and the characteristics of different ventilators. Given the limited space, we will concentrate our discussion on some key concepts and recent developments in the MV strategies for infants evolving from RDS to BPD.

3.4.1. The “open lung” concept

The RDS pathophysiology and lung mechanics decided that the RDS lungs are hard to open, and easy to collapse. Therefore applying CPAP or PEEP either via non-invasive support or intubated MV is important and effective in recruiting the lungs and maintain the FRC [36,37]. Once the lungs in a RDS infant are successfully recruited, maintaining an “open lung” is an important lung protective ventilation concept to prevent the evolvement of RDS into BPD. The open lung strategy helps to distribute the tidal ventilation during traditional MV evenly throughout the lungs and avoid the sheer stress from repeated collapse and reopening of the alveoli.

In MV, the “open lung” is mainly achieved through applying adequate PEEP or utilizing mean airway pressure (MAP) in high frequency oscillatory ventilation (HFOV) [38,39]. Unfortunately, many clinician are afraid of PEEP. Some NICUs even have a set policy that will not allow the PEEP to be set above 6 cmH₂O. Unfortunately, there are very limited data to help guide the selection of optimum PEEP. A recent Cochrane review only identified 4 trials of a total of 72 patients and suggested that using an oxygenation-guided lung recruitment maneuver might be helpful in selecting PEEP levels [40].

3.4.2. Conventional mechanical ventilation (CMV) vs. high frequency ventilation (HFV)

CMV, generally referred as positive pressure ventilation targeting the physiological range of tidal breathing, has been the standard MV method for infants with RDS. In comparison, HFV utilizes supra-physiological frequencies with much smaller tidal volumes (V_T) that is close to the airway dead-space volume and much lower inflation pressure at the alveolar level. Although initially introduced as potential strategy to reduce ventilator induced lung injury, HFOV has mainly been used as a rescue mode in the neonates and young infants. Data from recent years suggest that HFOV is an effective way of lung recruitment and early use of HFOV as a primary mode, rather than a rescue mode of MV, in preterm infants with RDS may result in a small reduction in the risk of BPD when compared with CMV [41]. However, as the authors of the 2014 Cochrane review pointed out, this evidence is weakened by the inconsistency of this effect across trials and counteracted by an increased risk of acute air leak (fixed-effect model summary RR 1.19, 95% CI 1.05 to 1.34; summary RD 0.04, 95%CI 0.01 to 0.07; NNTH25, 95%CI 14 to 100). Most of the studies reported similar short and long-term neurodevelopmental outcome of HFOV as compared to CMV. However, few trials showed an increase in severe intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL) in the HFOV groups [42,43] while some others showed a reduction in the risk of cerebral palsy [44]. It is also hard to compare the effects of HFOV with CMV on short and long-term pulmonary and neurodevelopmental outcomes when the open lung strategy is utilized. Even less data exist that compare the use of HFOV and CMV in infants with evolving BPD or compare the other commonly used HFV, the high frequency Jet Ventilation (HFJV) with CMV in terms of BPD prevention. Therefore, the selection of CMV vs. HFV in infants with RDS and evolving BPD remained at the discretion of the clinicians at the present time.

3.4.3. Modes of MV in infants with RDS and evolving BPD

There are various kinds of ventilators and mode of ventilation currently available to the clinicians to choose from. However, high quality data to guide this choice in this patient population are limited. Many physicians would like to have a “cookbook” recipe of best ventilator settings for these infants. Unfortunately, as we have discussed earlier, due to the complex interaction between lung developmental stages at birth and the timing of various post-natal influences and injuries, these infants' lung pathology and pulmonary mechanics are constantly changing and at different pace. Therefore the choice of best ventilator modality and settings needs to be individualized and also adapt to the change in each patient. In this section, we will discuss some key features of MV that need to be considered when providing MV

support to preterm infants with RDS that are evolving into BPD.

3.4.3.1. Non-synchronized vs. synchronized support. Modern neonatal ventilators are capable of synchronize positive pressure support from the ventilator with patient's spontaneous breathing efforts. Synchronized MV provides several advantages that is very important for this patient population: 1) improve ventilation efficiency by utilizing patient's own breathing efforts, and avoid the ventilator breath and patient's breath to go against each other; 2) minimize sedation and muscle paralysis need by improving patient's comforts; 3) reduce air leak and duration of MV [45]. There are several triggering mechanisms available in the modern ventilators. Currently, most neonatal ventilators use flow triggering mechanism. To best deliver synchronized breath in a preterm infants, clinicians need to pay attention to several details: 1) best to use a ventilator with a proximal flow sensor to ensure easy sensing and quick response time; 2) meticulous care of the flow sensor with timely cleaning and recalibration to avoid malfunctioning of the flow sensor; 3) Choose the appropriate triggering sensitivity. In a rapidly breathing premature infant, decreasing triggering sensitivity to reduce respiratory rate is not recommended as this will only increase the infant's work of breathing without addressing the underlying cause leading to tachypnea.

3.4.3.2. Modes of synchronized ventilation. There are several modes of synchronized ventilation that clinicians can choose from. Some commonly used modes in the neonates include synchronized intermittent mandatory ventilation (SIMV), Assist control (AC), Pressure support ventilation (PSV) or a combination of SIMV + PSV or CPAP + PSV. Table 2 summaries the features of SIMV, AC and PSV as the primary support mode and listed the advantages and disadvantages of each mode. It is important to set appropriate triggering sensitivity when using these synchronized ventilation modes. Inappropriately set low triggering sensitivity can lead to under detect of patient's spontaneous breathing and ventilators will deliver mandatory IMV breath without synchronization. Patient-ventilator asynchrony will result in increased work of breathing (WOB), agitation, and uneven/inefficient ventilation. On the contrary, inappropriately set high triggering sensitivity, especially in the presence of ETT leak, may lead to auto-triggering of the ventilator and as a result, over ventilation.

As previously discussed, the lung pathology and pulmonary mechanics changes over time from RDS to BPD. Therefore the ventilator mode of choice and the settings needs to adapt to patient's change. For example, the AC mode may be appropriate for a preterm infant with RDS in the early postnatal days when the baby has a more homogenous lung disease. However, when the lung disease evolve towards BPD with heterogenous aeration (i.e. areas of atelectasis and areas of hyperinflation or cystic changes), AC mode with a fixed short T_i may not be adequate to ventilate the areas with a long time constant. PSV mode may also have similar problems in an infant with heterogeneous lung disease or when higher P_{AW} is required to maintain an open lung. As a result, the combination mode of SIMV + PSV is frequently utilized. However, the ventilator settings needs to be adjusted over time. In the early postnatal days, a faster rate (30–40 times/minute) with a shorter T_i (0.3–0.4s), V_T of 4–6 ml/kg and PEEP of 5–8 CM are usually appropriate to ventilate an infant with RDS. The pressure support level can initially be set at slightly lower than the PIP required to deliver the targeted V_T . Later, when the lung pathology changes towards heterogenous lung disease, longer inspiratory and expiratory time may be needed to ventilator the areas with long time constant and higher V_T as well as PEEP maybe necessary to compensate for increased dead-space, overcome airway malacia and maintain FRC. Therefore, a strategy with lower SIMV rate (10–25 times/minute), longer T_i (0.5–0.8s) with higher V_T and PEEP might be more appropriate [4].

3.4.3.3. Volume-targeted ventilation vs. pressure-limited ventilation. Pressure-limited ventilation has been the main state of

Table 2
Features of SIMV, AC and PSV as the primary support modes.

	SIMV	AC	PSV
Cycling mechanism	Time-cycled based on preset Ti and RR	Time-cycled based on preset Ti	Flow-cycled based on preset % peak inspiratory flow
Preset settings	PIP or V _T , Ti, rate and PEEP, triggering level	PIP or V _T , Ti, PEEP, triggering level, and backup rate	PIP or V _T , PEEP, triggering level, and backup rate
Spontaneous breath	- Ventilator synchronize with detected spontaneous efforts to deliver preset number of breath; - Spontaneous breath in excess of the set rate supported only by PEEP	- Every detected spontaneous breath supported according to preset PIP or target V_T - Every inspiration controlled by a fixed Ti	- Every detected spontaneous breath supported according to preset PIP or target V_T - Variable Ti
Mandatory breath	Given when no spontaneous effort is detected during a triggering window based on the preset rate	Given when no spontaneous effort is detected during a triggering window based on the preset minimum backup rate	Given when no spontaneous effort is detected during a triggering window based on the preset minimum backup rate
Weaning	Gradual decrease of rate and inflation pressure	Gradual decrease of inflation pressure to reduce the level of support	Gradual decrease of inflation pressure to reduce the level of support
Advantage	Improve patient comfort as compared to no synchronization	All spontaneous breath supported leading to more consistent V _T and lowered WOB as compared to SIMV	- Patient determined Ti allows complete synchrony - Automatically adjust Ti with lung mechanics changes
Disadvantage	Uneven support of spontaneous breaths may result in variable V _T and high WOB in small preterms	- Under support if infant becomes apneic and backup rate set too low (usually set at 30–40 for small preterms) - Over ventilation if infant breathing too fast - Fixed Ti may worsen uneven ventilation in different lung areas	- Patient determined Ti is usually short, which may lead to low mean airway pressure (P_{AW}) and atelectasis unless PEEP is appropriately adjusted - Substantial leak from ETT may affect triggering

WOB: work of breathing, Ti: inspiration time, V_T: tidal volume, PIP: peak inspiratory pressure, PEEP: positive end expiratory pressure.

conventional MV in the neonates for many years. However, with the rapid change in lung compliance in an infant with RDS pre and post surfactant and over the course of the first few days and weeks after birth, volume-targeted ventilation (VTV) may be more appropriate. VTV aims to produce a stable tidal volume and thus avoid volutrauma due to lung overdistension and decrease the incidence of hypoxemia. A Cochrane meta-analysis that included 16 parallel studies and 4 crossover trials demonstrated that infants ventilated with VTV modes had reduced rates of death or BPD, pneumothoraces, hypocarbia, severe cranial ultrasound pathologies and duration of ventilation compared with infants ventilated with PLV modes [46].

One mode of VTV is Volume Guarantee (VG) in which the micro-processor compares exhaled tidal volume of the previous breath to the desired target V_T set by the operator, and adjusts the inspiratory pressure up or down to achieve that V_T. The choice of an appropriate V_T level is crucial and based on weight, postnatal age and underlying diseases. The most appropriate V_T level for preterm infants with RDS has not been determined, mostly 4–6 ml/kg. The smallest infants usually require a higher tidal volume (5.5–6 ml/kg for infants < 750 g) than bigger infants due to proportional larger instrumental dead spaces [47,48]. It has been shown that preterm infants with RDS who were ventilated with low V_T of 3 ml/kg, as compared to 5 ml/kg, had increased levels of pro-inflammatory cytokines and required longer duration of MV [49]. A several week-old preterm infants with evolving BPD may also need larger TV (5.5–6.5 ml/kg) for a combination of increased anatomical and alveolar dead space [48]. In a randomized crossover study, Hunt et al. compared the WOB under different V_T levels of 4 ml/kg to 7 ml/kg in 18 preterm infants born at < 32 weeks' gestation that remained ventilated beyond the 1st weeks of life (7–60 days of age). They found that only a V_T target of 7 ml/kg were able to reduce WOB below baseline in this group of infants with evolving BPD or established BPD [50].

Other than conventional ventilation mode, HFOV mode can work with volume guarantee as well. However, it has not been proven whether HFOV + VG offers short and long-term advantages over HFOV alone or CMV + VG. Further studies are needed to demonstrate the long-term neurodevelopmental effects of VTV and identify which VTV strategy offers the best long-term outcomes for preterm infants with RDS.

3.4.3.4. Neurally adjusted ventilatory assist (NAVA). NAVA provides

synchronized respiratory support by detecting the electrical activity of the diaphragm instead of the traditional flow or pressure triggering mechanism. It provides inspiration assist in proportion to the strength of the electrical signal captured from the diaphragm. There are some evidence that NAVA improves patient-ventilator synchrony and short-term oxygenation [51,52]. In a retrospective study of 29 preterm infants who were on MV for over 4 weeks, Jung et al. reported improved oxygen saturation, significantly lower FiO₂ requirements, lower ventilator support settings with improved blood gas values after transition from SIMV to NAVA [53]. In another retrospective study, the same group reported that NAVA can facilitate reduction in sedative use and decrease the frequency of cyanotic episodes in preterm infants on chronic MV [54]. However, data on longer term outcomes are lacking. A recent Cochrane review only included one RCT, which compared NAVA to patient-triggered time-cycled pressure-limited ventilation and found no significant difference in the duration of MV or incidence of BPD, pneumothorax or IVH [51].

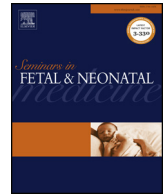
4. Conclusion

The goal of respiratory support in a preterm with RDS and evolving into BPD is to provide adequate support for growth and development while avoiding or minimizing lung injury. Both non-invasive and invasive respiratory support can be utilized. However the selection of proper mode of support and the support settings will vary based on each patient's pathophysiology and pulmonary mechanics, and needed to be weighed against the potential risks.

References

- [1] Mendelson CR. Role of transcription factors in fetal lung development and surfactant protein gene expression. *Annu Rev Physiol* 2000;62:875–915.
- [2] Hamvas A, Heins HB, Guttentag SH, Wegner DJ, Trusgnich MA, Bennet KW, et al. Developmental and genetic regulation of human surfactant protein B in vivo. *Neonatology* 2009;95(2):117–24.
- [3] Zuo YY, Veldhuizen RA, Neumann AW, Petersen NO, Possmayer F. Current perspectives in pulmonary surfactant—inhibition, enhancement and evaluation. *Biochim Biophys Acta* 2008;1778(10):1947–77.
- [4] Zhang HFW. Management of the infant with bronchopulmonary dysplasia assisted ventilation of the neonate. sixth ed. Elsevier; 2016. p. 380–90.
- [5] Kraybill EN, Runyan DK, Bose CL, Khan JH. Risk factors for chronic lung disease in infants with birth weights of 751 to 1000 grams. *J Pediatr* 1989;115(1):115–20.
- [6] Garland JS, Buck RK, Allred EN, Leviton A. Hypocarbia before surfactant therapy appears to increase bronchopulmonary dysplasia risk in infants with respiratory

- distress syndrome. *Arch Pediatr Adolesc Med* 1995;149(6):617–22.
- [7] Graziani LJ, Spitzer AR, Mitchell DG, Merton DA, Stanley C, Robinson N, et al. Mechanical ventilation in preterm infants: neurosonographic and developmental studies. *Pediatrics* 1992;90(4):515–22.
 - [8] Fujimoto S, Togari H, Yamaguchi N, Mizutani F, Suzuki S, Sobajima H. Hypocarbica and cystic periventricular leukomalacia in premature infants. *Arch Dis Child Fetal Neonatal Ed* 1994;71(2):F107–10.
 - [9] Kregenow DA, Swenson ER. The lung and carbon dioxide: implications for permissive and therapeutic hypercapnia. *Eur Respir J* 2002;20(1):6–11.
 - [10] Coakley RJ, Taggart C, Greene C, McElvaney NG, O'Neill SJ. Ambient pCO₂ modulates intracellular pH, intracellular oxidant generation, and interleukin-8 secretion in human neutrophils. *J Leukoc Biol* 2002;71(4):603–10.
 - [11] Masood A, Yi M, Lau M, Belcastro R, Shek S, Pan J, et al. Therapeutic effects of hypercapnia on chronic lung injury and vascular remodeling in neonatal rats. *Am J Physiol Lung Cell Mol Physiol* 2009;297(5):L920–30.
 - [12] Erickson SJ, Graueg A, Gurrin L, Swaminathan M. Hypocarbica in the ventilated preterm infant and its effect on intraventricular haemorrhage and bronchopulmonary dysplasia. *J Paediatr Child Health* 2002;38(6):560–2.
 - [13] Mariani G, Cifuentes J, Carlo WA. Randomized trial of permissive hypercapnia in preterm infants. *Pediatrics* 1999;104(5 Pt 1):1082–8.
 - [14] Carlo WA, Stark AR, Wright LL, Tyson JE, Papile LA, Shankaran S, et al. Minimal ventilation to prevent bronchopulmonary dysplasia in extremely-low-birth-weight infants. *J Pediatr* 2002;141(3):370–4.
 - [15] Woodgate PG, Davies MW. Permissive hypercapnia for the prevention of morbidity and mortality in mechanically ventilated newborn infants. *Cochrane Database Syst Rev* 2001(2):CD002061.
 - [16] Kaiser JR, Gauss CH, Williams DK. The effects of hypercapnia on cerebral autoregulation in ventilated very low birth weight infants. *Pediatr Res* 2005;58(5):931–5.
 - [17] Victor S, McKeering CM, Roberts SA, Fullwood C, Gaydecki PA. Effect of permissive hypercapnia on background cerebral electrical activity in premature babies. *Pediatr Res* 2014;76(2):184–9.
 - [18] Scher MS, Richardson GA, Salerno DG, Day NL, Guthrie RD. Sleep architecture and continuity measures of neonates with chronic lung disease. *Sleep* 1992;15(3):195–201.
 - [19] Ambalavanan N, Van Meurs KP, Perritt R, Carlo WA, Ehrenkranz RA, Stevenson DK, et al. Predictors of death or bronchopulmonary dysplasia in preterm infants with respiratory failure. *J Perinatol* 2008;28(6):420–6.
 - [20] Van Marter LJ, Allred EN, Pagano M, Sanocka U, Parad R, Moore M, et al. Do clinical markers of barotrauma and oxygen toxicity explain interhospital variation in rates of chronic lung disease? The Neonatology Committee for the Developmental Network. *Pediatrics* 2000;105(6):1194–201.
 - [21] Garland JS. Strategies to prevent ventilator-associated pneumonia in neonates. *Clin Perinatol* 2010;37(3):629–43.
 - [22] Fischer HS, Buhner C. Avoiding endotracheal ventilation to prevent bronchopulmonary dysplasia: a meta-analysis. *Pediatrics* 2013;132(5):e1351–60.
 - [23] Schmolzer GM, Kumar M, Pichler G, Aziz K, O'Reilly M, Cheung PY. Non-invasive versus invasive respiratory support in preterm infants at birth: systematic review and meta-analysis. *BMJ* 2013;347:f5980.
 - [24] Committee on F, Newborn, American Academy of P. Respiratory support in preterm infants at birth. *Pediatrics* 2014;133(1):171–4.
 - [25] Owen LS, Manley BJ. Nasal intermittent positive pressure ventilation in preterm infants: equipment, evidence, and synchronization. *Semin Fetal Neonatal Med* 2016;21(3):146–53.
 - [26] Lemyre B, Laughon M, Bose C, Davis PG. Early nasal intermittent positive pressure ventilation (NIPPV) versus early nasal continuous positive airway pressure (NCPAP) for preterm infants. *Cochrane Database Syst Rev* 2016;12:CD005384.
 - [27] Lemyre B, Davis PG, De Paoli AG, Kirpalani H. Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for preterm neonates after extubation. *Cochrane Database Syst Rev* 2017;2:CD003212.
 - [28] Ekhuagere O, Patel S, Kirpalani H. Nasal intermittent mandatory ventilation versus nasal continuous positive airway pressure before and after invasive ventilatory support. *Clin Perinatol* 2019;46(3):517–36.
 - [29] Lee J, Kim HS, Jung YH, Shin SH, Choi CW, Kim EK, et al. Non-invasive neurally adjusted ventilatory assist in preterm infants: a randomised phase II crossover trial. *Arch Dis Child Fetal Neonatal Ed* 2015;100(6):F507–13.
 - [30] Lee BK, Shin SH, Jung YH, Kim EK, Kim HS. Comparison of NIV-NAVA and NCPAP in facilitating extubation for very preterm infants. *BMC Pediatr* 2019;19(1):298.
 - [31] Hong H, Li XX, Li J, Zhang ZQ. High-flow nasal cannula versus nasal continuous positive airway pressure for respiratory support in preterm infants: a meta-analysis of randomized controlled trials. *J Matern Fetal Neonatal Med* 2019:1–8.
 - [32] Fleeman N, Dundar Y, Shah PS, Shaw BN. Heated humidified high-flow nasal cannula for preterm infants: an updated systematic review and meta-analysis. *Int J Technol Assess Health Care* 2019;35(4):298–306.
 - [33] Manley BJ, Roberts CT, Froisland DH, Doyle LW, Davis PG, Owen LS. Refining the use of nasal high-flow therapy as primary respiratory support for preterm infants. *J Pediatr* 2018;196:65–70 e1.
 - [34] Li J, Li X, Huang X, Zhang Z. Noninvasive high-frequency oscillatory ventilation as respiratory support in preterm infants: a meta-analysis of randomized controlled trials. *Respir Res* 2019;20(1):58.
 - [35] Chen L, Wang L, Ma J, Feng Z, Li J, Shi Y. Nasal high-frequency oscillatory ventilation in preterm infants with respiratory distress syndrome and ARDS after extubation: a randomized controlled trial. *Chest* 2019;155(4):740–8.
 - [36] da Silva WJ, Abbasi S, Pereira G, Bhutani VK. Role of positive end-expiratory pressure changes on functional residual capacity in surfactant treated preterm infants. *Pediatr Pulmonol* 1994;18(2):89–92.
 - [37] Dargaville PA, Tingay DG. Lung protective ventilation in extremely preterm infants. *J Paediatr Child Health* 2012;48(9):740–6.
 - [38] van Kaam AH, Rimensberger PC. Lung-protective ventilation strategies in neonatology: what do we know—what do we need to know? *Crit Care Med* 2007;35(3):925–31.
 - [39] Clark RH, Slutsky AS, Gerstmann DR. Lung protective strategies of ventilation in the neonate: what are they? *Pediatrics* 2000;105(1 Pt 1):112–4.
 - [40] Bamat N, Fierro J, Wang Y, Millar D, Kirpalani H. Positive end-expiratory pressure for preterm infants requiring conventional mechanical ventilation for respiratory distress syndrome or bronchopulmonary dysplasia. *Cochrane Database Syst Rev* 2019;2:CD004500.
 - [41] Cools F, Offringa M, Askie LM. Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants. *Cochrane Database Syst Rev* 2015;3:CD000104.
 - [42] High-frequency oscillatory ventilation compared with conventional intermittent mechanical ventilation in the treatment of respiratory failure in preterm infants: neurodevelopmental status at 16 to 24 months of postterm age. The HIFI Study Group. *J Pediatr* 1990;117(6):939–46.
 - [43] Moriette G, Paris-Llado J, Walth H, Escande B, Magny JF, Cambonie G, et al. Prospective randomized multicenter comparison of high-frequency oscillatory ventilation and conventional ventilation in preterm infants of less than 30 weeks with respiratory distress syndrome. *Pediatrics* 2001;107(2):363–72.
 - [44] Truffert P, Paris-Llado J, Escande B, Magny JF, Cambonie G, Saliba E, et al. Neuromotor outcome at 2 years of very preterm infants who were treated with high-frequency oscillatory ventilation or conventional ventilation for neonatal respiratory distress syndrome. *Pediatrics* 2007;119(4):e860–5.
 - [45] Greenough A, Dimitriou G, Prendergast M, Milner AD. Synchronized mechanical ventilation for respiratory support in newborn infants. *Cochrane Database Syst Rev* 2008(1):CD000456.
 - [46] Klingenberg C, Wheeler KI, McCallion N, Morley CJ, Davis PG. Volume-targeted versus pressure-limited ventilation in neonates. *Cochrane Database Syst Rev* 2017;10:CD003666.
 - [47] Nassabeh-Montazami S, Abubakar KM, Keszler M. The impact of instrumental dead-space in volume-targeted ventilation of the extremely low birth weight (ELBW) infant. *Pediatr Pulmonol* 2009;44(2):128–33.
 - [48] Keszler M, Nassabeh-Montazami S, Abubakar K. Evolution of tidal volume requirement during the first 3 weeks of life in infants < 800 g ventilated with Volume Guarantee. *Arch Dis Child Fetal Neonatal Ed* 2009;94(4):F279–82.
 - [49] Lista G, Castoldi F, Fontana P, Reali R, Reggiani A, Bianchi S, et al. Lung inflammation in preterm infants with respiratory distress syndrome: effects of ventilation with different tidal volumes. *Pediatr Pulmonol* 2006;41(4):357–63.
 - [50] Hunt K, Dassios T, Ali K, Greenough A. Volume targeting levels and work of breathing in infants with evolving or established bronchopulmonary dysplasia. *Arch Dis Child Fetal Neonatal Ed* 2019;104(1):F46–9.
 - [51] Rossor TE, Hunt KA, Shetty S, Greenough A. Neurally adjusted ventilatory assist compared to other forms of triggered ventilation for neonatal respiratory support. *Cochrane Database Syst Rev* 2017;10:CD012251.
 - [52] Shetty S, Hunt K, Peacock J, Ali K, Greenough A. Crossover study of assist control ventilation and neurally adjusted ventilatory assist. *Eur J Pediatr* 2017;176(4):509–13.
 - [53] Jung YH, Kim HS, Lee J, Shin SH, Kim EK, Choi JH. Neurally adjusted ventilatory assist in preterm infants with established or evolving bronchopulmonary dysplasia on high-intensity mechanical ventilatory support: a single-center experience. *Pediatr Crit Care Med* 2016;17(12):1142–6.
 - [54] Lee J, Kim HS, Jung YH, Choi CW, Jun YH. Neurally adjusted ventilatory assist for infants under prolonged ventilation. *Pediatr Int* 2017;59(5):540–4.



Transitioning from an ICU ventilator to a portable home ventilator

Julie L. Fierro*, Howard B. Panitch

Division of Pulmonary Medicine, Children's Hospital of Philadelphia, 3401 Civic Center Blvd, Philadelphia, PA 19104, United States

ARTICLE INFO

Keywords:

Mechanical ventilation
Chronic respiratory failure
Home mechanical ventilation

ABSTRACT

There is a variety of portable ventilators on the market, each with its' own features. A clinician needs to understand the unique characteristics of the ventilators available in his or her region, as well as the nuances of primary and secondary settings for these portable home ventilators in order to create a comfortable breath that allows for adequate gas exchange for the patient. Understanding the interplay of the portable home ventilator and the ventilator circuit is also a key component of transitioning a patient to a portable home ventilator. This review details characteristics of some of the more commonly used machines in the United States, as well as the settings to be considered in supporting a child with chronic respiratory failure outside of the hospital. As more patients are being discharged from the hospital with mechanical home ventilation, new ventilators are being developed that expand upon features of current machines.

Making the transition to a portable home ventilator (PHV) is often one of the last major steps prior to discharge for a patient requiring long term mechanical ventilation. Some considerations when making this transition include the timing of changing support from the ICU ventilator to a portable model, the choice of what type of PHV and circuit is most appropriate for a patient, and the ventilator settings necessary to allow the patient to breathe comfortably and naturally while supporting his or her breathing in the most appropriate manner.

The optimal time to transition to a PHV is determined by the patient's condition and the anticipated time to discharge. The patient should be medically stable, weaned off inhaled gases such as nitric oxide or helium-oxygen, and if appropriate, gaining weight well and able to tolerate therapies on current ventilator settings. The child should also have a stable airway, whether that is the natural airway or tracheostomy. If the transition is made too soon and the patient does not tolerate the transition well, it may be unclear to the medical team if this is due to an issue related to the PHV and ventilator settings or a confounding factor related to an underlying medical condition. The child should be supported by the PHV for at least 2 weeks before discharge, with no changes made to ventilator settings over that period of time. Ideally, the actual ventilator that the child will use outside of the hospital should be used for several days before discharge to make sure no adjustments are necessary.

1. Factors to consider when selecting a PHV

The current generation of PHVs can support most patients

adequately, but children who are very small or weak, or who have severe obstructive or restrictive lung disease occasionally require support that is unique to certain machines. Thus, one must consider not only the patient's medical condition and his or her ventilator needs, but also any limitations of the ventilator.

If the signal to end inspiration cannot be adjusted adequately, some patients can experience ventilator asynchrony with difficulty cycling a breath, particularly if there is a large leak in the circuit. For instance, the LTV® ventilator series (CareFusion) can only be adjusted to a cycle sensitivity of 40% of peak flow for Pressure Support breaths. If an excessive leak does not permit a reduction in flow to that level, then inspiration will be prolonged and its termination requires a backup time termination setting.

A final consideration when selecting a PHV is the familiarity of the community nurses and respiratory therapists with a particular machine. As new ventilators come to market, it will take time for clinicians and respiratory therapists to feel comfortable using these machines and training caregivers on how to manage them in the outpatient setting.

2. Types of circuits

The ventilator circuit connects the ventilator to the patient. It can include tubing for separate inhalation and exhalation limbs, a humidifier or heat/moisture exchanger, an exhalation valve or port, a pressure and/or flow measuring device, inline filters, and adaptors for delivering medications [1]. The proximal part of the circuit is connected to the patient via a tracheostomy (invasive modality) or mask/

* Corresponding author.

E-mail addresses: fierroj@email.chop.edu (J.L. Fierro), panitch@email.chop.edu (H.B. Panitch).

<https://doi.org/10.1016/j.siny.2019.101041>

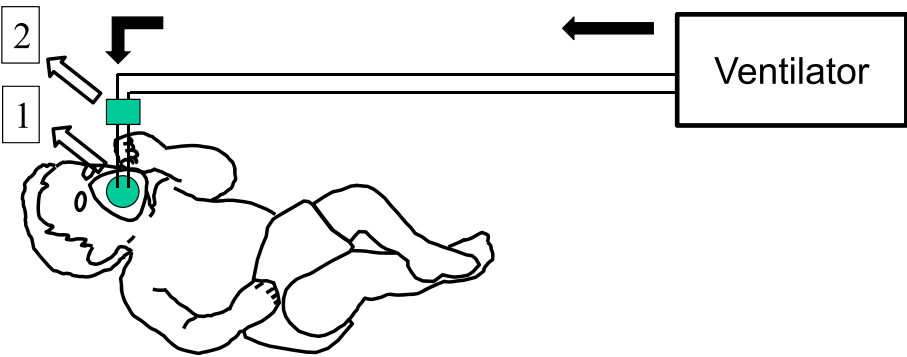


Fig. 1. Ventilation via passive circuit. Fresh gas from the ventilator is delivered to the patient through a single limb circuit (solid arrows) and exhaled gas travels through the same tubing (open arrows). The passive circuit has no active exhalation valve, and so exhaled gas leaves the circuit through a fixed leak in the circuit, either via an intentional leak in a mask (1) or into an orifice within the circuit tubing (2).

mouthpiece (non-invasive modality). There are 3 types of respiratory circuits that are determined by the type of exhalation device used and whether pressure or flow is monitored. Choosing between specific types of circuits will be based on the type of ventilator to be used, ventilator settings and mode requirements of the patient, special features that are only available with certain circuit configurations, and how narrowly FiO_2 must be regulated.

2.1. Passive circuit

The passive circuit has no active exhalation valve, and so exhaled gas leaves the circuit “passively” through a fixed leak in the circuit. It uses a single tube for both inspiration and exhalation. An intentional leak is built either into a mask or into an orifice within the circuit tubing created by a device such as a Whisper Swivel (Respironics) placed close to the patient’s airway. Exhalation occurs through this intentional leak point (Fig. 1).

Because the passive circuit does not contain a true nonrebreathing expiratory valve and the inspiratory and expiratory paths share a single limb, there is a risk for rebreathing carbon dioxide when exhaled gas becomes part of the following breath’s delivered tidal volume [2]. To avoid this, the ventilator delivers a continuous flow of fresh gas during exhalation at a rate high enough to wash out the dead space of the circuit. The expiratory pressure setting (positive end expiratory pressure (PEEP) or expiratory positive airway pressure (EPAP)) determines the leak rate (flow) across the exhalation port. Since the resistance across the expiratory opening is fixed, by Ohm’s law, pressure and flow will be proportional to each other. Thus, the minimum expiratory pressure must be high enough to create adequate flow to wash out the circuit dead space. If the expiratory pressure were set too low so that it could not wash out the dead space of the circuit, a portion of the exhaled gas would accumulate in the ventilator tubing. With the patient’s next breath, rebreathing of CO_2 would occur, thereby increasing dead space ventilation [3].

Tidal volume is not measured directly in a passive circuit. Rather, an algorithm is used that estimates the exhaled tidal volume while taking into consideration the flow delivered to the patient and the leak flow through the port [4]. However, as has been shown in multiple studies, the algorithm used to determine the leak and tidal volume differs among homecare ventilators; tidal volume is underestimated and this

underestimation increases in the setting of larger circuit leaks [5–7].

A major benefit of a passive circuit is its ability to compensate for unintentional leaks in delivering the preset pressure by adjusting flow to achieve the set pressures. While these ventilators make up for unintentional leak in pressure control (PC) modes, the Respironics Trilogy can also compensate for unintentional leaks in volume control (VC) modes. To compensate for an unintentional leak, the ventilator constantly monitors pressure and flow outputs during each breath, and adjusts ventilator output on the subsequent breath based on that feedback. This type of leak compensation is not available for circuits with active expiratory valves. It is important to note that when using a low flow oxygen source to deliver an FiO_2 greater than ambient air, an increase in air flow from the ventilator in response to a variable leak will dilute the concentration of oxygen being delivered and can be detrimental for patients who are sensitive to supplemental oxygen delivery.

An additional advantage of a passive circuit is that it allows for use of some ventilator setting options like trigger and cycle algorithms (i.e. Auto-Trak with the Philips Respironics Trilogy) and volume-targeted pressure modes (Average Volume Assured Pressure Support (AVAPS) or Intelligent Volume Assured Pressure Support (iVAPS)), which will be discussed in additional detail below. Finally, a passive circuit involves less tubing for caregivers to have to handle and manipulate, making it lighter and less burdensome as compared to a double limb circuit (Table 1).

2.2. Active pressure and flow circuits

There are two types of active circuits: the active proximal airway pressure (PAP) circuit and the active flow circuit (Fig. 2A and B). The **active PAP** circuit is a single limb circuit with two small pressure lines. One pressure line monitors proximal airway pressure while the second connects to an active expiratory valve (i.e., a mushroom valve or diaphragm valve) which opens on exhalation and closes on inspiration. The active PAP circuit measures the inspiratory tidal volume.

The **active flow** circuit can be assembled in either a single limb or a double limb configuration. The double limb circuit includes an inspiratory and expiratory limb: the distal ends are connected to the inspiratory and expiratory ports of the ventilator, respectively, and the proximal ends are connected to a Y-piece terminating at the patient

Table 1
Features to consider when choosing a circuit.

Passive Circuit	Active Circuit
Single limb	Single limb (active PAP/active flow) or double limb (active flow)
Positive expiratory pressure is mandatory	EPAP/PEEP are optional
Flow trigger; Specific ventilator trigger algorithms are available	Flow or pressure trigger
Variable FiO_2	Constant FiO_2
Tidal volume is estimated	Tidal volume is measured
Volume-targeted modes available (AVAPS (Respironics)/iVAPS (ResMed))	Limited volume-targeted modes (Pressure Support with Volume Guarantee (ResMed))

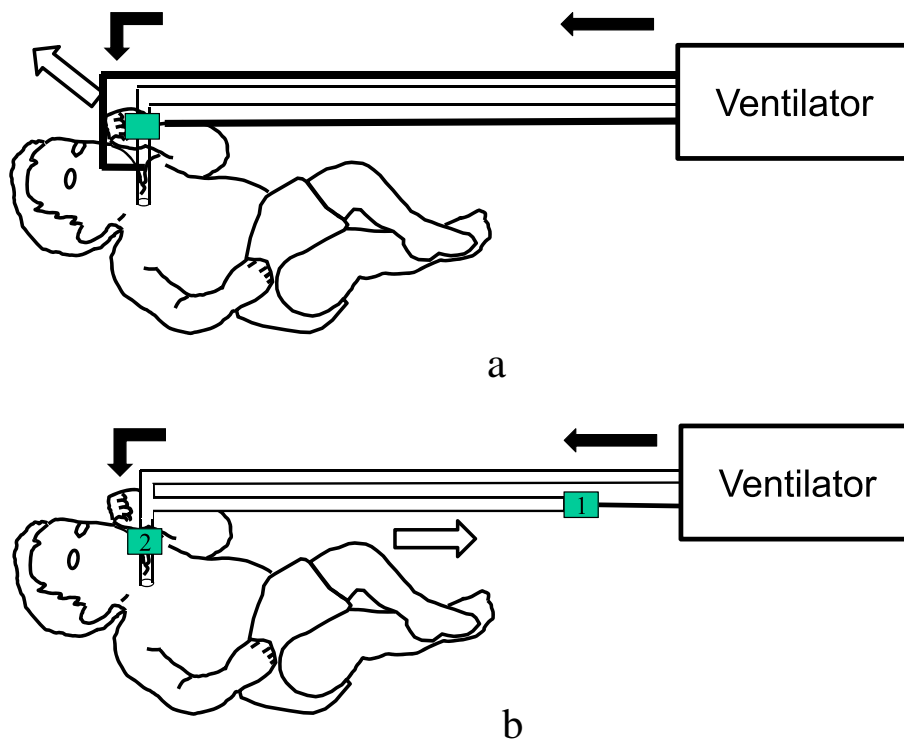


Fig. 2. Ventilation via active circuits. A: The active PAP circuit is a single limb circuit with two small pressure lines, one measuring proximal airway pressure while the second connects to an expiratory valve that opens on exhalation and closes on inspiration. Fresh gas from the ventilator is delivered to the patient through a single limb circuit (solid arrows) and exhaled gas exits the circuit through the active valve (open arrow). B: The active flow circuit includes an inspiratory and expiratory limb. Fresh gas from the ventilator is delivered to the patient through the inspiratory limb (solid arrows) and exhaled gas exits the circuit through the expiratory valve (open arrow) (1). The distal ends of the circuit are connected to the inspiratory and expiratory ports of the ventilator, respectively, and the proximal ends are connected in a Y-piece terminating at the patient interface. Flow is measured either close to the patient interface (2) or via a sensor in the ventilator (not pictured).

interface. The flow sensor is located at different points in the circuit depending on the PHV; it may be located in-line just distal to the airway opening (Phillips Trilogy, Hamilton-T1, CareFusion LTV®), or at the ventilator (ResMed Astral™).

An active circuit limits the use of some ventilator algorithms. For example, with the ResMed Astral™ and the Phillips Respironics Trilogy ventilators, certain algorithms can only be used with a passive circuit (VSync, AVAPS, iVAPS, Auto-Trak) [8,9].

One advantage of active circuits is that the use of EPAP or PEEP is optional. A passive leak circuit requires continuous flow through the valve during exhalation, which is generated by setting a positive expiratory pressure. The active PAP circuit eliminates CO₂ via a non-rebreathing expiratory valve, whereas the active flow circuit includes a non-rebreathing valve or a second limb for exhalation; thus the concerns related to rebreathing of CO₂ that can occur with passive circuits are no longer present.

In contrast to the variable FiO₂ generated in passive circuits, active circuits provide consistent delivery of supplemental oxygen. The FiO₂ delivered through an active circuit remains constant since flow does not increase to compensate for unintentional leaks.

Another attribute of active circuits is their ability to measure, rather than estimate, the delivered tidal volume. The active PAP circuit measures inhaled tidal volume whereas the active flow circuit measures exhaled tidal volume.

Finally, just as some features of a PHV are only available when using a passive circuit, other features are only offered with an active circuit. Many home ventilators can deliver volume-controlled breaths (i.e., Volume Control-Assist/Control or Volume Control- Synchronized Intermittent Mandatory Ventilation) only when an active circuit is used; one exception to this is the Respironics Trilogy, which can provide Volume Control ventilation with all circuit configurations. The use of an active flow circuit with the ResMed Astral™ ventilator allows for a greater range of flow triggers, down to 0.5 LPM, and also allows for use of a pressure trigger [9] (Table 1).

2.3. Limitations of circuit options based on available PHV

A passive/single limb circuit cannot be used with a Hamilton-T1 or CareFusion LTV® ventilator since each uses a closed circuit with an expiratory limb; even small unintentional leaks will cause these systems to alarm. An active circuit can be used with all currently available PHVs.

3. Features of PHVs

There have been major advances in the design of home care ventilators including the ability to provide continuous flow, an increasing number of available modes of ventilation, lighter weight machines, and machines with longer internal battery life. Machine characteristics, including the range of outputs, available modes, range of sensitivities to trigger and cycle assisted breaths, and other special features all differ between manufacturers and even between different models from the same company. An understanding of these characteristics is critical for making the best match between a PHV and the patient.

3.1. Basic features of PHVs

All of the current PHVs are approved for children weighing 5 kg or more. Newer ventilators are lighter weight, adding to the ease of portability [8,10–12] (Table 2). The internal battery life and availability of external batteries that can extend the time away from an electrical power source determine the ease with which patients can leave their homes, travel a distance to get to appointments, or maintain ventilator support at home in areas with frequent power outages. Manufacturer statements about estimated battery life are based on support of an adult with fairly low ventilatory needs; thus, actual duration of battery life may be a good deal shorter in patients who require high pressures or rates of positive pressure breaths.

The number of prescriptions available on the PHV that can be preset by the practitioner can potentially reduce user error in the case of a

Table 2
Basic features of PHVs.

	LTV® (CareFusion)	Trilogy (Philips Respironics)	Astral™ (ResMed)	Hamilton	Vivo 65 (Breas)
Weight (kg)	6.6	5	3.2	4.9	5.3
Internal battery (hours)	1	3	8	4	3.5
External battery (hours)	6	3	16 (Two 8 h batteries)	4 (2nd 4 h battery)	8
Available Prescriptions	1	2	2–4	1	3

Table 3
Primary settings of PHVs.

	LTV® (CareFusion)	Trilogy (Philips Respironics)	Astral™ (ResMed)	Hamilton	Vivo 65 (Breas)
PIP maximum (cm H ₂ O)	99	50	50	60	35
PEEP (or EPAP) maximum (cm H ₂ O)	20	25	20	35	20
Ti min (sec)	0.3	0.3	0.2	0.2	0.3
Bias Flow (LPM)	10	Variable (up to 200)	Variable (up to 250)	3	5

patient who requires different ventilator settings routinely under different conditions, i.e., for mouthpiece ventilation during waking hours and nasal ventilation during sleep, or in the case of a patient who has regular and “sick day” ventilator settings.

3.2. Primary settings

Pressure and volume control modes are available for all of the current PHVs; however, there is variation in terms of the upper or lower limits of these settings across machines (Table 3). For example, the peak inspiratory pressure of the Philips Respironics Trilogy and ResMed Astral™ ventilators (the sum of the baseline PEEP/EPAP and the inflating pressure above the PEEP/EPAP) is limited to 50 cm H₂O, which may be restricting in a child with high airway resistance or low respiratory system compliance. The amount of PEEP required to support a patient could influence the choice of PHV. Most machines can deliver a PEEP up to 20 cm H₂O, but some patients, like those with severe bronchopulmonary dysplasia who can have high intrinsic PEEP or severe tracheomalacia, may require higher levels of PEEP and so will need a machine that can provide this necessary support [13,14]. Finally, the bias flow in a CareFusion LTV® and Hamilton-T1 ventilator is constant whereas the Philips Respironics Trilogy and ResMed Astral™ have variable flow.

When transitioning from an ICU ventilator to a PHV, the clinician needs to select a mode of ventilation. A ventilator assists breathing through either pressure control (PC) or volume control (VC) modes. The control variable refers to the function that is preset, or prescribed, by the clinician. PC means the breaths are pressure constant and volume variable, whereas VC means the breaths are volume constant and pressure variable [15].

VC ventilation via PHVs may not be possible if there is a large leak around the tracheostomy tube, or if the desired tidal volume is small. When a child receiving invasive ventilation has a large peri-tracheal leak, delivery of a breath in VC mode can lead to hypoventilation as the preset volume of air leaks out of the system and inadequate pressure is generated to move the chest [16]. Usually, this problem is averted by switching to a PC mode; PC ventilation overcomes such leaks better than VC ventilation by increasing ventilator output until the targeted pressure is reached [16–18]. The Respironics Trilogy ventilator, however, has an algorithm that will compensate for such leaks when the ventilator is set in VC mode using a passive circuit, but other machines do not have such software and that leak compensation is not available with active circuits. If a VC mode of ventilation is preferred, the usual alternative is to switch the patient's tracheostomy tube to a cuffed model so that any leak can be minimized. Since unintentional leaks are common in the case of patients using non-invasive ventilation or those with an uncuffed tracheostomy tube, transitioning these patients to PC

ventilation on the PHV may be preferable.

While most machines can deliver a preset tidal volume as small as 50 mL, the inspiratory time is constrained by the prescribed tidal volume and the flow is determined by algorithms of the ventilator that cannot be adjusted. For instance, the PHV will restrict the maximum inspiratory time of a 50 or 60 mL breath to 0.3 s. Thus, a 5 kg infant with bronchopulmonary dysplasia who was supported by a tidal volume of 60 mL and an inspiratory time of 0.7 s on the ICU ventilator would have to receive the same tidal volume over 0.3 s via the PHV. There are several pressure-regulated volume-targeted modes that are offered on PHVs, as discussed below, that can circumvent this problem. Alternatively, switching to PC ventilation allows the clinician to set the inspiratory time as desired.

The compliance of the ventilator circuit can become a significant factor when a child supported in a Volume Control mode is receiving a small tidal volume. The circuit compliance could result in a discrepancy between the delivered tidal volume to the patient and that tidal volume measured by the ventilator due to the compressible volume of gas in the circuit. These differences are negligible when the set tidal volume is large relative to the compressible volume of the circuit, but when the set tidal volume is relatively small this difference can result in hypoventilation [19,20]. Some ventilators have the option of automatic circuit compliance compensation during setup; this function measures the compressible volume and compensates for it.

Due to the potential for variations in volumes delivered through PC modes, newer strategies include volume targeted modes that can be used during pressure support (PS) ventilation. In the case of the Philips Respironics Trilogy ventilator, the AVAPS (Average Volume Assured Pressure Support) feature maintains a specified tidal volume by adjusting the pressure support. The PS is varied between a preset IPAP minimum and maximum. The ventilator averages tidal volume over 5 min and changes PS up or down gradually over several breaths to maintain this tidal volume [8]. The AVAPS feature is only accessible with a passive circuit configuration. The ResMed Astral™ has a volume assurance mode called iVAPS (Intelligent Volume-Assured Pressure Support) that targets a patient's pre-calculated alveolar ventilation and changes settings breath to breath within a prescribed range to maintain an alveolar ventilation target. This mode is not recommended for patients who weigh < 30 kg, and it also can only be used with a passive circuit. The ResMed Astral™ also has a Pressure Support with Safety Volume mode; the PS changes breath to breath based on a targeted tidal volume, allowing for a more consistent tidal volume to be delivered with each breath [9]. The mode can be used in any sized patient, including infants, and it is available for use with both passive and active flow circuits. The authors have been able to support even critically ill infants with severe bronchopulmonary dysplasia or pulmonary hypoplasia using this modality, often at lower mean airway and peak

inspiratory pressures than those required when using the ICU ventilator.

When transitioning to PC ventilation with a PHV, reviewing the peak inspiratory pressure the patient achieved over a range of time (such as when asleep or with activity) will allow for determination of the approximate peak pressure setting that is required on the PHV. Constraints around pressure settings for home ventilation are determined by the limits of the machine, as mentioned above. There is no threshold or absolute value of either peak inspiratory pressure or PEEP that would preclude a discharge to home, as long as the equipment chosen can provide the necessary support. We have discharged patients safely who have required PEEP values of 20 cmH₂O or higher because of severe intrinsic PEEP, as long as they have demonstrated a period of stability on that support before hospital discharge. It makes little sense to wean a patient to some arbitrary value before home discharge to make a practitioner more comfortable, when the maneuver only makes the patient less stable.

4. Creating a comfortable breath on a PHV

Establishing the secondary settings of a PHV allows the clinician to create a comfortable, yet effective breath for the patient. These phase variables set the terms for the breath the patient is receiving. They are defined as the *trigger* which initiates inspiration; the *limit* which is a predetermined goal of ventilator output that cannot be exceeded; the *cycle* which switches the breath from inspiration to exhalation and back to the baseline variable (PEEP or EPAP). Adjustment of these variables should be made while observing the interaction between the patient and ventilator with regards to synchrony, comfort, and gas exchange. Trigger and cycle variables apply to both spontaneous and mandatory ventilator breaths [21].

4.1. Trigger variable

A ventilator-assisted breath can be triggered, or initiated, either by the ventilator or the patient. Trigger variables used by current PHVs include time, flow, pressure, and special algorithms. Machine- and patient-triggered breaths can exist in the same scheme of ventilator support, i.e. when Synchronized Intermittent Mandatory Ventilation (SIMV) is used with Pressure Support Ventilation (PSV). In the case of the machine-triggered breath, the clinician sets a desired respiratory rate and breaths are delivered according to this preset frequency. For example, if the mandatory respiratory rate is set to 10 bpm, the patient receives a ventilator-delivered breath every 6 s. In the case of SIMV, the ventilator-delivered breath is synchronized with the patient's inspiratory effort to allow for more comfortable breath delivery [22].

Patient initiated breaths can be signaled by flow, pressure, or specific ventilator algorithms. Flow-triggered breaths are initiated when the patient's inspiratory effort creates a flow equal to or greater than a preset flow threshold. The change in flow is detected by a flow sensor in the circuit [23]. The flow trigger sensitivity settings vary by machine. In the case of the CareFusion LTV® and Philips Respironics Trilogy, the range for the flow trigger sensitivity is 1–9 LPM; the ResMed Astral™ offers a wider range (0.5–15 LPM), depending on circuit configuration. The option of having a lower flow threshold can be useful for young infants, children with neuromuscular weakness, or patients with severe obstructive lung disease as these conditions can make it more difficult for them to generate the flow necessary to trigger the ventilator.

The Trilogy ventilator also has two algorithms that combine information about volume, flow, and flow pattern to determine when a breath should be initiated and terminated, referred to as Auto-Trak and Auto-Trak[Sensitive]. In addition to analyzing and comparing the shape of the flow pattern of the patient's signal against calculated curves, Auto-Trak requires 6 mL of air to be moved by the patient, while Auto-Trak[Sensitive] requires the patient to move 3 mL of air [8].

The goal of an appropriate trigger is to reduce the amount of work

required for a patient to receive positive pressure assistance while minimizing the delay between the time the patient attempts to trigger a breath and the machine delivers the support. This must be balanced with trying to prevent auto-triggering, which is the delivery of a positive pressure breath based on an erroneous flow signal, usually related to an unintentional leak. PHVs with a passive respiratory circuit can compensate for an unintentional leak and overcome issues related to auto-triggering [4]. This can also be accomplished with the CareFusion LTV®, which requires an active circuit. When the leak compensation option is turned on, it adjusts the baseline flow to compensate for a patient circuit leak up to 6 LPM of flow. By setting the sensitivity (flow trigger) above the machine reported leak, triggering is improved in the presence of a circuit leak [10].

The rise time also plays an important role in patient comfort and synchrony. The rise time determines the speed with which a ventilator reaches a set peak inspiratory pressure during PC or PS breaths. This is the time required to change from the baseline pressure to 90% of the peak pressure [24]. The rise time can be adjusted on PHVs, in increments starting at 0.1 s. The higher the number, the slower is the rate of rise to peak pressure [8]. The CareFusion LTV® utilizes a term called 'profile' with available profiles (rise times) ranging from 0.1 to 1 s. Each step up in the profile between 1 and 9 causes an increase in the rise time of 33% over the previous setting. For example, a profile of 1 is 0.1 s and 2 is 0.13 s [10]. Clearly, if the rise time is set too long relative to the inspiratory time, the ventilator may not be able to reach the desired peak pressure.

4.2. Limit variable

The limit variable is a predetermined variable that limits inspiration. That is, the variable cannot be superseded but it does not terminate (cycle) the breath [25]. For example, a PS breath will be *pressure limited and flow cycled*, meaning that when the breath is triggered the pressure will rise to the preset value and remain there until inspiratory flow decreases to a predetermined percentage of the peak flow, after which the pressure returns to the baseline value. Similarly, during a PC breath, the pressure rises to the preset value and remains there until a preset time elapses (*pressure limited and time cycled*). As noted above, current PHVs permit delivery of breaths with both pressure and volume limits, sometimes within the same mode of ventilation (e.g. VC-SIMV with PSV).

4.3. Cycle variable

The cycle variable ends the inspiratory phase of a breath (i.e., cycles off inspiration). A breath can be cycled by one of several variables including time, flow, volume, or pressure [23]. A breath is considered time cycled when it terminates after a prescribed inspiratory time. Traditionally, this inspiratory time is applied to mandatory breaths delivered by the ventilator [4]. For example, an inspiratory time of 0.8 s means that inspiratory flow or pressure is provided for 0.8 s after which the ventilator cycles, or terminates inspiration, and switches to the exhalation phase. If the inspiratory time is longer than that required by the patient, he or she may want to exhale and be unable to do so, resulting in cycle asynchrony. It is important to consider that in a PC mode, the tidal volume is determined by the set pressure, the inspiratory time and the respiratory system mechanics. In the case of a patient with respiratory system mechanics that require a longer inspiratory time to fill (e.g. a high resistance or high compliance system), a longer inspiratory time should be set on the ventilator to achieve the desired tidal volume [23]. A longer inspiratory time will also be useful in infants with established severe bronchopulmonary dysplasia who have heterogeneous regional time constants (the product of resistance and compliance) [13].

There are modes of ventilation that allow for time cycling of patient-triggered breaths. This is the case for the Philips Respironics Trilogy

ventilator in PC mode where both patient- and machine-triggered breaths are time cycled [8]. The ResMed Astral™ ventilator, like many other ResMed machines, offers an option to have an inspiratory maximum time and minimum time set allowing for spontaneous breaths that would normally be flow cycled to be time cycled within a prescribed inspiratory time range if flow cycling would fall outside of that range [9]. Establishing a minimum inspiratory time for patients with stiff chest walls or other causes of short respiratory system time constants, where flow cycling of PS breaths would result in a small tidal volume, can increase inspiratory time and increase the tidal volume. Some machines, like the CareFusion LTV® or the ResMed Astral™, provide a backup time cycle setting (e.g. Time Termination or T_i max) that will terminate a breath after a specified time if the flow cycle threshold is never met (see below). This typically occurs in the setting of a large unintentional leak.

Flow cycling occurs when the inspiratory flow of a spontaneous breath falls to a preset percentage of the peak flow, at which point the ventilator switches to the exhalation phase. The percentage of peak flow at which this occurs can be adjusted on most PHVs, and the chosen threshold is referred to as the cycle sensitivity. For example, a cycle sensitivity of 80% means that when the flow falls to 80% of the peak inspiratory flow, the ventilator cycles to exhalation. The flow cycle will need to be adjusted if the operator observes that the ventilator cycles after the patient's inspiratory effort ends, or if the operator wants to support the patient through a larger percentage of inspiration [23]. It is also important to note that when using a flow cycle, a leak in the ventilator circuit can lead to a lack of decline in the flow signal resulting in an excessively prolonged inspiratory time and ventilator asynchrony [26].

Pressure cycling occurs when a preset peak airway pressure is reached which cycles a breath. This is typically an alarm situation, or safety feature (high pressure alarm), that is set to prevent barotrauma. Volume cycling occurs in a volume controlled mode and takes place when a prescribed volume is preset [23].

5. Future directions

The world of home mechanical ventilation is quickly expanding. As the medical field continues to advance, patients are surviving with chronic illnesses that can progress to subacute or chronic respiratory failure resulting in the need for home mechanical ventilation.

New ventilators are being developed that expand on currently available home ventilator modes, offer greater trigger sensitivity, and extend the lower size range of suitable patients. As new devices and equipment come to market, it will be important that caregivers and providers can be appropriately trained on these devices prior to their entering the homecare setting.

Another exciting direction for home mechanical ventilation is the role of telemedicine. Several studies have shown the potential safety and efficacy of using telemedicine for children supported at home by mechanical ventilation. [27,28] As this path continues to be explored, it may prove to be a very useful and convenient assessment tool for caregivers, especially those who live at considerable distance from the site of the Home Ventilation Program, and providers.

6. Conclusion

The transition from an ICU ventilator to a portable home ventilator requires significant planning and thoughtfulness with regards to the equipment selected and settings used on the PHV. Recognizing the advantages and disadvantages of each component in the system can mean the difference between successful transition to a home machine and failure, with extended hospitalization. Building a comfortable breath for the patient that allows for adequate gas exchange requires knowledge of the secondary settings of the PHV. As the field of home mechanical ventilation continues to grow, providers and caregivers will

need to be equipped with the necessary tools to manage complex patients and life sustaining equipment in the home setting.

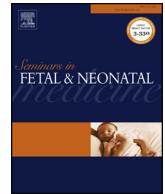
Declaration of competing interest

Within the last 3 years, Howard B. Panitch was a consultant to Philips Respironics for their development of a portable ventilator for mass casualty and home care use. He has no extramural funding.

Julie L Fierro does not have any conflicts of interest or any funding sources to report.

References

- [1] [Chapter 53]: Fighting the Ventilator Tobin M, Jubran A, Laghi F, editors. Principles and practice of mechanical ventilation. 3 ed. New York, NY: McGraw-Hill; 2013.
- [2] Szulmowski Z, Belkhouja K, Le QH, Robert D, Argaud L. Bilevel positive airway pressure ventilation: factors influencing carbon dioxide rebreathing. *Intensive Care Med* 2010;36(4):688–91.
- [3] Ferguson GT, Gilmartin M. CO₂ rebreathing during BiPAP ventilatory assistance. *Am J Respir Crit Care Med* 1995;151(4):1126–35.
- [4] Gregoretti C, Navalesi P, Ghannadian S, Carlucci A, Pelosi P. Choosing a ventilator for home mechanical ventilation. *Breathe* 2013;9(5).
- [5] Contal O, Vignaux L, Combescure C, Pepin JL, Joliet P, Janssens JP. Monitoring of noninvasive ventilation by built-in software of home bilevel ventilators: a bench study. *Chest* 2012;141(2):469–76.
- [6] Fauroux B, Leroux K, Pépin JL, Lofaso F, Louis B. Are home ventilators able to guarantee a minimal tidal volume? *Intensive Care Med* 2010;36(6):1008–14.
- [7] Luján M, Sogo A, Pomares X, Monsó E, Sales B, Blanch L. Effect of leak and breathing pattern on the accuracy of tidal volume estimation by commercial home ventilators: a bench study. *Respir Care* 2013;58(5):770–7.
- [8] Respironics P. Trilogy 100 clinical manual. https://aeroflowinc.com/wp-content/themes/genisis_child_theme/files/Trilogy100PatientManual.pdf.
- [9] ResMed. Astral series user guide. https://www.resmed.com/us/dam/documents/products/machine/astral-series/user-guide/astral-100-150_user-guide_amer_eng.pdf.
- [10] LTV series ventilator operator manual. 2005.
- [11] Published Hamilton T1 operator's manual. 2015 Accessed.
- [12] Vivo 65 clinician's manual. In.
- [13] Abman SH, Collaco JM, Shepherd EG, et al. Interdisciplinary care of children with severe bronchopulmonary dysplasia. *J Pediatr* 2017;181:12–28. e11.
- [14] Napolitano N, Jalal K, McDonough JM, et al. Identifying and treating intrinsic PEEP in infants with severe bronchopulmonary dysplasia. *Pediatr Pulmonol* 2019 Jul;54(7):1045–51. <https://doi.org/10.1002/ppul.24328>. Epub 2019 Apr 4.
- [15] Richard D, Branson B, RRT, Robert S, Campbell R. RRT. Modes of ventilator operation. In: Neil MacIntyre M, Richard D, Branson B, editors. Mechanical ventilation. Philadelphia, PA: W.B. Saunders Company; 2001. p. 51–84.
- [16] Gilgoff IS, Peng RC, Keens TG. Hypoventilation and apnea in children during mechanically assisted ventilation. *Chest* 1992;101(6):1500–6.
- [17] Smith IE, Shneerson JM. A laboratory comparison of four positive pressure ventilators used in the home. *Eur Respir J* 1996;9(11):2410–5.
- [18] Highcock MP, Shneerson JM, Smith IE. Functional differences in bi-level pressure preset ventilators. *Eur Respir J* 2001;17(2):268–73.
- [19] Hess D, McCurdy S, Simmons M. Compression volume in adult ventilator circuits: a comparison of five disposable circuits and a nondisposable circuit. *Respir Care* 1991;36(10):1113–8.
- [20] Richard D, Branson B, RRT. RRT. The patient-ventilator interface: ventilator circuit, airway care, and suctioning. In: Neil MacIntyre M, Richard D, Branson B, editors. Mechanical ventilation. Philadelphia, PA: W.B. Saunders Company; 2001. p. 85–101.
- [21] Chatburn RL, El-Khatib M, Mireles-Cabodevila E. A taxonomy for mechanical ventilation: 10 fundamental maxims. *Respir Care* 2014;59(11):1747–63.
- [22] Bernstein G, Heldt GP, Mannino FL. Increased and more consistent tidal volumes during synchronized intermittent mandatory ventilation in newborn infants. *Am J Respir Crit Care Med* 1994;150(5 Pt 1):1444–8.
- [23] Chatburn R, Mireles-Cabodevila E. Chapter 3. Basic principles of ventilator design. In: Tobin MJ, editor. Principles and practice of mechanical ventilation. third ed. New York, NY: McGraw-Hill; 2013.
- [24] Blakeman TC, Rodriguez D, Hanseman D, Branson RD. Bench evaluation of 7 home-care ventilators. *Respir Care* 2011;56(11):1791–8.
- [25] Chatburn RLB, RRT FAARC, Branson RDB. RRT. Classification of mechanical ventilators. Mechanical ventilation. Philadelphia, PA: WB Saunders Company; 2001.
- [26] Calderini E, Confalonieri M, Puccio PG, Francavilla N, Stella L, Gregoretti C. Patient-ventilator asynchrony during noninvasive ventilation: the role of expiratory trigger. *Intensive Care Med* 1999;25(7):662–7.
- [27] Casavant DW, McManus ML, Parsons SK, Zurkowski D, Graham RJ. Trial of telemedicine for patients on home ventilator support: feasibility, confidence in clinical management and use in medical decision-making. *J Telemed Telecare* 2014;20(8):441–9.
- [28] Miyasaka K, Suzuki Y, Sakai H, Kondo Y. Interactive communication in high-technology home care: videophones for pediatric ventilatory care. *Pediatrics* 1997;99(1):E1.



Practical use of telemedicine in the chronically ventilated infant

John Chuo^{a,*}, Kathleen A. Webster^b

^a Children's Hospital of Philadelphia, Philadelphia, PA, USA

^b Advocate Children's Hospital Oak Lawn, IL, USA

ABSTRACT

Telemedicine, or the use of electronic communication technology to improve patient health, is becoming more widely adopted as a means of bringing together patients, providers and family members to facilitate evaluation, monitoring, diagnosis and treatment. A particularly vulnerable group consists of children with dependence on technology, such as chronic mechanical ventilation. This chapter will provide an overview of how telehealth technology is currently being used, for supporting this patient population through 1) inpatient support 2) integration with the medical home 3) bridging care transitions 4) remote patient management and 5) multispecialty consultations. We will also discuss the impact on quality and cost, the current research environment and practical points for implementation into clinical practice.

1. Introduction

Telemedicine can be broadly defined as the use of electronic communications to exchange medical information in order to improve the health of the patient. The evolution of technology from simple voice (telephone) or text-based communications to our current state, in which audio, video, monitors, sensors, and peripheral devices are used to bring together various combinations of patients, provider and family members to facilitate evaluation, monitoring, diagnosis and treatment. Children today incorporate technology into their lives with a frequency and ease previous generations never could have imagined. This is true even of our neonatal population, who may begin using telemedicine care even in the prenatal stages for evaluation and monitoring, and then transition throughout their early lives as telemedicine supports resuscitation, transport, specialty consultations, family support and remote training. Technology is used not just in telemedicine support, but increasingly in medical care to support children with complex medical needs. The Maternal Child Health Bureau recognizes Children with Special Health Care Needs (CSHCN) as those who require more care and resources on a chronic basis. Children with medical complexity represent about 5% of the US pediatric population (www.childhealthdata.org), [1]. Of these, approximately 600,000 are estimated to be dependent on medical technology such as mechanical ventilation, feeding tubes, oxygen and/or monitors [2]. Approximately 1/3 of those children are graduates from the neonatal intensive care unit and have formidable management and safety challenges – 50% are seen in the emergency department within 3 months of discharge, and are the highest risk for readmission within the first 2 weeks after discharge [2,3]. As these children leave the neonatal intensive care units and

transition to home, they continue to require the support of a coordinated care team including multiple specialists, primary care providers, nurses, case managers, therapists, nutritionists and others. Specialist availability, distance barriers and the cost and logistics of even short distance trips can be significant. The use of telehealth technology can help to achieve increased access and improved efficiency for this patient population through 1) inpatient support 2) integration with the medical home 3) bridging care transitions 4) remote patient management and 5) multispecialty consultations.

1.1. Inpatient telemedicine support

The American Academy of Pediatrics technical report on telemedicine offers insights into how telemedicine can be used to support neonates by increasing access to specialists and providing timely connections in urgent situations [4]. Support of both the neonate and the on-site team can be achieved with tele-resuscitation support. The use of telemedicine to remotely assist resuscitation of infants has been reported to improve adherence with Neonatal Resuscitation Protocol (NRP) standards and quality of the resuscitation [5,6]. A similar approach has helped identify and addressed gaps in resuscitation training [7–9]. The use of telemedicine throughout the neonatal course helps to lay the foundation for similar use in discharge planning and post discharge care for the chronically ventilated infant [10]. For infants, occupational and physical therapy can have positive neurodevelopmental impact that improves with repetitive exercise – therefore, using telemedicine tools to teach and coach caregivers to perform these exercises frequently with their baby could be beneficial.

* Corresponding author.

E-mail address: chuoj@email.chop.edu (J. Chuo).

<https://doi.org/10.1016/j.siny.2019.101036>

1.2. Integration into the medical home/bridging transitions

Planning a transition to home for a chronically ventilated infant begins with the patient centered medical home (PCMH). One of the core foundations for the PCMH is the use of health IT (<https://pcmh.ahrq.gov/page/pcmh-foundations>) which could include the use of telemedicine technology.

Applying this concept to children incorporates the core tenets of comprehensive care, expanded access, better communication, and coordinated care, along with partnership with the patient's family. The American Academy of Pediatrics recommends the patient centered medical home as an integral part of telemedicine implementation [11]. This begins with coordination between specialty care and primary care prior to discharge. A clear care plan should be developed and handed off to the primary care provider. This can be done through a telephone call, transmission of the electronic record and/or incorporate video handoff to allow assessment with both teams present in real time.

Studies looking at parental perceptions of home care for technology dependent children [12,13] have identified technical, social, emotional and financial concerns of parents as they navigate this transition. Parents report fear when they transition to home and lose the support of the hospital staff, as well as a need for a means to address gaps in knowledge or training. One way to address these needs is through post discharge follow up. A summary of 93 telemedicine "check in" visits shortly after discharge of complex surgical infants showed the feasibility of such check ins. The visits identified respiratory issues as amongst the top challenges faced by caregivers once they are home with their baby [14]. Parents often have questions about home monitors, oxygen and CPAP interfaces and usage. Using interactive telemedicine technology can help to facilitate real time troubleshooting of such equipment and education.

1.2.1. Transition to PCP

Transition of infants who are dependent on respiratory support from the NICU to the primary care provider can be challenging, especially those with 2 or more chronic conditions, and complex hospital courses. The use of telemedicine to perform patient handoffs from neonatal intensivists to primary care providers could have potential benefits, depending on the patient's conditions, medical complexity, and the provider's experience with caring for similar patients in the practice.

1.3. Remote patient management

Once an infant has successfully transitioned to home, there is still need for ongoing training and support which can be augmented by use of telemedicine. Parents of technology dependent children report a need for support of babysitters and others who may try to provide respite care, fearing knowledge gaps in home care staff and a need for reassurance from a trusted provider who is familiar with their child [12]. As described earlier, telemedicine has been used to support neonatal resuscitation in the delivery room and other inpatient environments. Interestingly, the severity and complexity of unresolved medical conditions present on discharge that are left to be managed in the ambulatory setting has risen [15]. The potential risk for needing remote and acute assistance with sicker children at home has increased. Progress in this offers encouraging prospects for using telemedicine to assist healthcare professionals in the home management of ventilator Assisted individuals (VAI), such as children with skeletal dysplasia and thoracic insufficiency. Similar use in adults with chronic obstructive pulmonary disease have noted that while telemedicine can facilitate earlier intervention when needed, it can also lead to increased hospitalizations, face-to-face visits, or home care visits. A more comprehensive cost benefit analysis is needed, perhaps at the level of condition subgroups.

In addition to acute situations, the decision to recommend in-person visits and emergency department referrals for medically complex

children is based often on incomplete information without visual aids. The logistics of transporting a chronically ventilated child has its safety risks as well as cost in human resources, time and money. Using telemedicine technology to assess these patients at home may help to provide both the parent and provider with enough information for earlier intervention and decide whether an in-person visit is justified. One such home program utilized audio and video connection to allow children on home ventilator support to connect to their care team. This intervention allowed the children to be cared for in the home. The use of telemedicine allowed improved clinical decision making and increased parent confidence in the assessment and treatment recommendations [16]. This program provided real time visual assessment of children in their homes. This care will be further augmented in the future as technology continues to advance with development of devices that will allow assessment of heart and breath sounds, temperature, otoscope examination, blood pressure, blood glucose and other parameters [17].

In a study of such a device with medically complex children, the ability to perform a parent facilitated exam was not only possible, but provided additional information and helped to both provide guidance for home care and detect critical needs that would not have been picked up by phone [18].

1.3.1. Pulmonary care

Infants with thoracic insufficiencies, airway secretion issues present a formidable pulmonary toilet problem. Published literature in adults and older children with similar issues have shown cautious promise where provider were able to prescribe chest physiotherapy promptly, associated with reduce hospitalization and emergency room admissions [10].

1.3.2. Pulmonary function testing

Monitoring spirometry and pulse oximetry in children with cystic fibrosis remotely and more frequently results in improved outcomes as well as significant cost savings [19]. Due to the flexibility of telemedicine technology and use, programs can be designed to suit the unique needs of different patient groups and individuals.

1.3.3. Ventilator management

While today's home ventilators have capability to transmit patient data, how best to utilize this technology that would lead to improved patient outcomes or healthcare quality remains to be determined. Organizations like American Thoracic Society and European Respiratory Society have recognized the potential positive impact of such tools but caution the need for scientific investigation of usefulness regarding patient outcomes and equipment reliability [20,21].

1.3.4. Medication management

Ref. [22] Implementation of antimicrobial stewardship program is a pivotal practice element for healthcare institution. We developed a remote infectious disease consultancy program via telemedicine in a high-specialized pediatric cardiac hospital. A consultation for antibiotic strategy for each patient was available via telemedicine in addition to biweekly discussion of all clinical cases. Aim of this study was to evaluate the impact of the remote stewardship program in terms of a) appropriateness of antibiotic prescription; b) incidence of multi-resistant infection; and c) cost. A 'before - after' study was performed comparing the period immediately before starting the program and one year after. There was a trend in the reduction of nosocomial infectious disease rate (9.5 vs 6.5 per 1000 person days), with a reduction in the overall antibiotic cost (25,000 vs 15,000 EUR) and in the average antibiotics packages used per admission (9 vs 6.7 packages). A significant reduction in the multi-drug resistant isolation rate was observed (104 vs 79 per 1000 person days, $p = 0.01$). In conclusion, the infectious disease meeting via telemedicine has been an effective tool for economic and professional development and multidisciplinary management of

complex patients. The appropriate use of antibiotics reduced the multi-drug resistant bacteria selection, thus improving patient safety.

1.4. Remote specialty consults

In addition to acute needs, routine assessments of the child in the home by both the primary provider and specialty consults may be of benefit. In some situations, remote visits to the home may be preferable to exams in an office setting. Having a child in a familiar environment provides invaluable insight, not only to physicians but also to therapists, counselors and other members of a medically complex child's healthcare team [23]. The ability to provide specialty services, such as pain management and palliative care have been shown to be feasible with associated cost savings and need for travel [24–26]. In school settings, these benefits were seen in addition to perceived reduction in stress for the child and increased likelihood of a successful exam [27,28].

Telemedicine can also be used to support multispecialty clinics. Chronically ventilated children may require multiple specialists and care team providers, and coordinated clinics have been shown to have many benefits, however barriers of time, space and logistics can make them cost prohibitive [29]. Allowing a child with multispecialty needs to attend a virtual clinic from home, school or a primary care office would break down many of these barriers and allow more availability and flexibility [30–32]. Providers can also communicate directly with primary providers or school staff to provide information and education as to the child's condition and needs.

1.5. Clinical limitations: physical examination

While in person examination remains the gold standard for obtaining the highest quality and most comprehensive physical examination, much can still be done remotely through visual inspection and/or the presence of a nurse or family member with the patient. Current telemedicine peripherals allow high quality remote auscultation, funduscopy, otoscopy, and high definition camera system that can zoom and pan to see pupillary reactions. Diagnostic peripherals allow for video EEG, EKG, spirometry, and ultrasound.

1.6. Logistic technological requirements, security, documentation and interoperability

Implementation of telemedicine requires certain system infrastructures to be in place [33] such as clinical champions, technical support, and reliable simple to use equipment.

Connectivity challenges which must be addressed include adequate bandwidth, interoperability of technology and firewall traversal. Using devices outside of the health system control must be evaluated from a security standpoint to ensure adequate protection of patient information. Technology support of both hardware and software in various settings is also a concern [26]. Testing, collaboration with information technology support and backup plans are an integral part of program development.

1.7. Impact on quality and cost

Quality. While the value proposition of telemedicine remains unclear as a complex equation of quality over cost. However, a practical approach for evaluating and monitoring program has been proposed by the National Quality Forum (NQF Quality Framework). Their domains like those offered by the Institute of Medicine quality address effectiveness, efficiency, timeliness, safety, patient centeredness, equity. The cost side of the equation includes financial, human resources, process, unused inventory, and “non-value added” effort and processes. Such differences can result in support challenges. Since medically complex patients incur > 60% of all children health care

expenditures [15], the potential cost savings are tremendous as long as safety is preserved. However, because the value equation is different for the various stakeholder groups (patient, provider, health system, practice, hospital, payers), unanimous support can be a challenge.

1.7.1. Cost and reimbursement

Cost effective in the ICU in certain populations [34]. Cost effective of “hospital at home” programs [35]. While many ventilated infants are insured by Medicaid, regulation details differ amongst states. Coverage depends on service offered and specialty services involved. Some states exclude coverage for store and forward technology or remote patient monitoring. Many states require a specific patient setting for care to be provided, and may exclude home or schools, while others do not recognize non-physician providers and or/may require the provider to be in a specific setting. Updates and details of state policies and telemedicine practices can be found at the Consortium of Telehealth Research Centers, funded by a HRSA Initiative (<https://www.telehealthresourcecenter.org/>).

Research

There is a “booming use” of telehealth without a corresponding “booming understanding” of its impact, advantages, and limitations. Formal research to answer such questions fall into one of three broad domains: clinical trials, implementation/quality science, and descriptive. The majority of Pediatric telehealth studies have described telehealth use in small cohorts and the very few that focus on ventilated infants involved newborn resuscitation [5]. In a small cohort of ventilated children described, telemedicine appeared to enable earlier diagnosis and treatment of life threatening events [36]. The American Academy of Pediatric Section on Telehealth Care have established research interest groups, one of which focuses on medically complex children, with hopes of identifying evidence based best telehealth practices through multicenter research (<https://www.aap.org/en-us/about-the-aap/Sections/Section-on-Telehealth-Care/Pages/SPROUT.aspx>).

Practice points

While research measuring impact of telehealth on ventilated assisted infants gains momentum, those wishing to use telehealth for ventilated infants could benefit from the Operating Procedures for Pediatric Telehealth [37].

Definitions. The geographical location of the patient and provider are termed, respectively, as the originating and distant (remote) site.

Security. The ATA Core Guidelines (<https://southwesttrc.org/sites/southwesttrc.org/files/ATA%20Core%20Guidelines.pdf>) describe standards for video and audio equipment used on mobile devices that includes installation of up-to-date antivirus software and security patches. “Medical grade” applications should be used and secured in accordance with existing privacy guidelines. Patient related information, including images, should not be sent via standard texting applications or stored on personal mobile devices.

Consent. Generally, states differ in terms of their opinion on consent, which is typically dependent on the situation (timing, condition, episode). In emergency situations, consent can often be waived. Legal representative should have knowledge of the telemedicine service compared with in-person care, billing arrangement, applicable credentials of the distant site provider. Patient verification should be done at each encounter. If encounters are to be recorded, providers should refer to state-specific laws, disclose that encounter will be recorded to parents/legal representatives and obtain written consent.

Encounter. Originating and remote sites must meet standards for privacy with minimal distraction and background noise. All

parties present should be introduced at the beginning of the encounter. No personal health information not belonging to the patient should be visible. Providers should routinely communicate with the patient's primary care provider about a telehealth encounter, especially on recommendations on care plan changes.

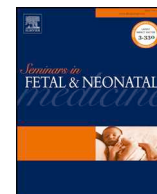
Licensure. Provider must have a valid professional practice license in the state where the patient is located at the time of the encounter. However, exception rules exist for certain circumstances according to state specific laws. Providers and their legal representatives should review credentials and privileges in accordance with local, state, and federal regulations at the remote and originating site.

Funding

Neither author has any significant financial relationship to disclose.

References

- [1] Elias ER, Murphy NA, Council D. On Children with, Home care of children and youth with complex health care needs and technology dependencies. *Pediatrics* 2012;129(5):996–1005.
- [2] Toly VB, et al. Neonates and infants discharged home dependent on medical technology: characteristics and outcomes. *Adv Neonatal Care* 2016;16(5):379–89.
- [3] Spicer A, et al. Health status and health service utilization of infants and mothers during the first year after neonatal intensive care. *Adv Neonatal Care* 2008;8(1):33–41.
- [4] Burke BL, et al. Telemedicine: pediatric applications. *Pediatrics* Jul 2015;136(1):e293–308. <https://doi.org/10.1542/peds.2015-1517>.
- [5] Fang JL, et al. The impact of telemedicine on the quality of newborn resuscitation: a retrospective study. *Resuscitation* 2018;125:48–55.
- [6] Donohue LT, Hoffman KR, Marcin JP. Use of telemedicine to improve neonatal resuscitation. *Children (Basel)* 2019;6(4).
- [7] Yang CP, et al. Can telemedicine improve adherence to resuscitation Guidelines for critically ill children at community hospitals? A randomized controlled trial using high-fidelity simulation. *Pediatr Emerg Care* 2017;33(7):474–9.
- [8] Butler L, et al. The impact of telemedicine on teamwork and workload in pediatric resuscitation: a simulation-based, randomized controlled study. *Telemed J e Health* 2019;25(3):205–12.
- [9] Escobedo MB, et al. Recent recommendations and emerging science in neonatal resuscitation. *Pediatr Clin N Am* 2019;66(2):309–20.
- [10] Garuti G, et al. Pulmonary rehabilitation at home guided by telemonitoring and access to healthcare facilities for respiratory complications in patients with neuromuscular disease. *Eur J Phys Rehabil Med* 2013;49(1):51–7.
- [11] Herendeen N, Deshpande P. Telemedicine and the patient-centered medical home. *Pediatr Ann* 2014;43(2):28–32.
- [12] Kirk S, Glendenning C. Developing services to support parents caring for a technology dependent child at home. *Child Care Health Dev* 2004;30(3):209–18.
- [13] Brenner M, et al. Parents' perspective of the transition to home when a child has complex technical needs. *Int J Integr Care* 2015;2015. <https://doi.org/10.5334/ijic.1852>. 15:e035.
- [14] Willard A, et al. Complex surgical infants benefit from postdischarge telemedicine visits. *Adv Neonatal Care* 2018;18(1):22–30.
- [15] Simon TD, et al. Children with complex chronic conditions in inpatient hospital settings in the United States. *Pediatrics* 2010;126(4):647–55.
- [16] Casavant DW, et al. Trial of telemedicine for patients on home ventilator support: feasibility, confidence in clinical management and use in medical decision-making. *J Telemed Telecare* 2014;20(8):441–9.
- [17] Beck Melinda. New gadgets that could give telemedicine a boost. *Wall Street J* 25 Sept 2016 <http://www.wsj.com/>, Accessed date: 12 October 2016.
- [18] Notario PM, et al. Home-based telemedicine for children with medical complexity. *Telemed J e Health* 2019.
- [19] Tagliente I, et al. Telemonitoring in cystic fibrosis: a 4-year assessment and simulation for the next 6 years. *Interact J Med Res* 2016;5(2):e11.
- [20] Ambrosino N, et al. Tele-monitoring of ventilator-dependent patients: a European respiratory society statement. *Eur Respir J* 2016;48(3):648–63.
- [21] Sterni LM, et al. An official American thoracic society clinical practice guideline: pediatric chronic home invasive ventilation. *Am J Respir Crit Care Med* 2016;193(8):16–35.
- [22] Ceradini J, et al. Telemedicine as an effective intervention to improve antibiotic appropriateness prescription and to reduce costs in pediatrics. *Ital J Pediatr* 2017;43(1):105.
- [23] Webster K. Telehealth in children with special needs. In: Rheuban KS, Krupinski EA, editors. *Understanding telehealth*. New York: McGraw Hill; 2017. p. 209–18.
- [24] Bradford BJ, Heald P, Petrie S. Health services for special needs children in Pennsylvania schools. *J Sch Health* 1994;64(6):258–60.
- [25] Bradford N, et al. Components and principles of a pediatric palliative care consultation: results of a Delphi study. *J Palliat Med* 2014;17(11):1206–13.
- [26] Katalinic O, Young A, Doolan D. Case study: the interact home telehealth project. *J Telemed Telecare* 2013;19(7):418–24.
- [27] Langkamp DL, McManus MD, Blakemore SD. Telemedicine for children with developmental disabilities: a more effective clinical process than office-based care. *Telemed J e Health* 2015;21(2):110–4.
- [28] McConnochie KM, et al. Effectiveness of telemedicine in replacing in-person evaluation for acute childhood illness in office settings. *Telemed J e Health* 2006;12(3):308–16.
- [29] Collaco JM, et al. Interdisciplinary pediatric aerodigestive care and reduction in health care costs and burden. *JAMA Otolaryngol Head Neck Surg* 2015;141(2):101–5.
- [30] Davis AM, et al. Treating rural pediatric obesity through telemedicine: outcomes from a small randomized controlled trial. *J Pediatr Psychol* 2013;38(9):932–43.
- [31] Slusser W, et al. Multidisciplinary pediatric obesity clinic via telemedicine within the Los Angeles metropolitan area: lessons learned. *Clin Pediatr (Phila)* 2016;55(3):251–9.
- [32] Wallace P, et al. Virtual outreach: a randomised controlled trial and economic evaluation of joint teleconferenced medical consultations. *Health Technol Assess* 2004;8(50):1–106. [iii-iv].
- [33] Olson CA, et al. The current pediatric telehealth landscape. *Pediatrics* 2018;141(3).
- [34] Yoo BK, et al. Economic evaluation of telemedicine for patients in ICUs. *Crit Care Med* 2016;44(2):265–74.
- [35] Cryer L, et al. Costs for 'hospital at home' patients were 19 percent lower, with equal or better outcomes compared to similar inpatients. *Health Aff (Millwood)* 2012;31(6):1237–43.
- [36] Munoz-Bonet JI, López-Prats JL, Flor-Macián EM, Cantavella T, Domínguez A, Vidal Y, et al. Medical complications in a telemedicine home care programme for paediatric ventilated patients. *J Telemed Telecare* 2019. <https://doi.org/10.1177/1357633X19843761>.
- [37] McSwain SD, et al. American telemedicine association operating Procedures for pediatric telehealth. *Telemed J e Health* 2017;23(9):699–706.



Tracheostomy decision making: From placement to decannulation

Frances Flanagan^{a,*}, Fiona Healy^b

^a Division of Pulmonary and Respiratory Diseases, Boston Children's Hospital, 333 Longwood Avenue, Boston, 02115, USA

^b Children's Health Ireland at Temple Street, Dublin 1, Ireland

ARTICLE INFO

Keywords:

Tracheostomy
Mechanical ventilation
Decannulation
Polysomnogram
Bronchoscopy

ABSTRACT

Over the last few decades, greater numbers of tracheostomies have been performed in medically complex and fragile children to manage upper airway obstruction, progressive neuromuscular disorders, abnormal ventilatory drive and to facilitate airway clearance. The optimal timing of tracheostomy tube placement and methods to determine suitable patients for the procedure remain unclear. Caring for children with tracheostomies can have a considerable financial and psychosocial impact on a family. Pediatric patients with tracheostomies have a 2–3 fold greater morbidity and mortality compared to adult patients. Clinicians should provide as much clarity as possible for families on the positive and negative aspects of pediatric tracheostomies and long term mechanical ventilation prior to tracheostomy placement. Tracheostomies are often placed as a bridge, whilst time for healing, growth and other therapies are needed to help overcome the indication for tracheostomy. Suitable investigations used to determine the optimal timing of decannulation remain physician and institution dependent.

1. Introduction

Tracheostomy was not commonly performed in children until the nineteenth century, when it was used at times of infectious epidemics including Poliomyelitis and Diphtheria [1]. With the introduction of vaccines and antibiotics, the main indication for tracheostomy has changed from infection to upper airway obstruction, progressive or irreversible neuromuscular disorders, abnormal ventilatory drive and to allow adequate airway clearance [2]. Tracheostomy is a common procedure in the adult intensive care unit (ICU), but is less common in the pediatric population, occurring in < 3% of pediatric ICU patients [3]. More children are surviving with chronic medical conditions, largely due to advances in technology including tracheostomy care with the majority of these children now cared for in their own home. Although a surgical tracheostomy provides a safe and protected airway, all procedures present potential risks and complications. Morbidity and mortality rates reported with tracheostomy insertion in pediatric patients are 2–3 times higher than in adults [4]. Therefore, the pros and cons of tracheostomy placement should be carefully considered for each individual patient and their family.

2. Considerations pre tracheostomy insertion

Many factors should be carefully considered by the medical team

prior to tracheostomy placement including; a thorough preoperative history and examination with the aim to identify factors which if addressed could avoid tracheostomy placement, optimal timing of the tracheostomy, caregiver education and ability to manage the patient in the home setting and the expected outcome of tracheostomy placement (whether a bridge to recovery and decannulation or long term tracheostomy).

2.1. Timing of tracheostomy placement

In the adult population, tracheostomies are considered if mechanical ventilation is required for more than 72 h, with a median occurring at day 9 of intubation & ventilation [3]. Early tracheostomy in the adult population was shown to reduce the risk of hospital acquired pneumonia, duration of mechanical ventilation, length of stay in the ICU and mortality rate [5]. There is no consensus on the optimal timing of tracheostomy insertion in the pediatric and neonatal population. Some preterm infants remain intubated for > 3 months prior to tracheostomy consideration [3]. A recent meta-analysis reported that early tracheostomy (performed within the first 7 days of endotracheal intubation) was associated with decreased duration of mechanical ventilation and length of stay in the ICU [5]. However, the pediatric populations included in the studies analyzed were not inclusive of all pediatric patients requiring a tracheostomy with some studies excluding neonatal

* Corresponding author.

E-mail addresses: frances.flanagan@childrens.harvard.edu (F. Flanagan), fiona.healy@cuh.ie (F. Healy).

<https://doi.org/10.1016/j.siny.2019.101037>

ICU patients [6]. Prolonged periods of intubation can interfere with normal development and may result in laryngotracheal damage [7,8]. Neonates often undergo many failed extubation trials prior to tracheostomy placement. Despite this, tracheostomies in the pediatric population are most frequently performed in the first year of life due to the increasing survival of preterm infants requiring long term ventilation [2].

The age at time of tracheostomy insertion differs based on the pathophysiology of the underlying disorder. Patients with airway obstruction, cardiopulmonary or craniofacial anomalies are typically younger at time of tracheostomy placement than those with traumatic injury or neurological impairment [2,9].

2.2. Indications for tracheostomy insertion

The development of immunizations and advances in neonatal care have led to a change in the primary indications for pediatric tracheostomy. Current common indications include facilitating long term ventilation, overcoming craniofacial abnormalities causing airway obstruction, subglottic stenosis, neurological impairment and providing access for airway clearance [10]. Neonates and infants are increasingly surviving with complex medical needs for whom tracheostomy and/or home mechanical ventilation is an integral part of their overall care [11,12]. The most common indication differs amongst institutions and countries, likely related to the availability of medical care and local infrastructure [13]. Gergin et al. described the changes in indication of tracheostomies over time in their institution with increasing numbers performed for cardiopulmonary reasons [2] (Fig. 1).

Traditionally, tracheostomy was viewed as a negative neonatal outcome, due to an assumed increased risk of death and impaired neurodevelopmental outcome in the preterm population [14]. However, causality is difficult to prove and bronchopulmonary dysplasia (BPD) and prolonged mechanical ventilation are themselves associated with neurodevelopmental impairment [15,16]. Luo et al. reported improved outcomes in short term changes in growth, respiratory support needs, tolerance of developmental therapy and daily sedation requirements after tracheostomy in infants with severe BPD [8]. They suggested that these benefits should be taken into consideration in infants requiring prolonged high-level respiratory support and balanced against the risks and caregiver burden of tracheostomy [8].

In some cases, a tracheostomy may be a temporary procedure to permit further treatment e.g. to facilitate mandibular distraction surgery in cases of micrognathia or retrognathia. Bannink described 4 patients with syndromic craniosynostosis who were successfully decannulated after midface advancement surgery [17]. In other cases, tracheostomy is considered a long term intervention with no expectations that developmental changes or growth will allow decannulation in

the future. This group typically includes children with permanent neurological or pulmonary conditions that require mechanical ventilation for survival. Clinicians should provide as much clarity as possible for families about the distinction between tracheostomy as a *bridge* or *destination* to avoid unrealistic expectations [18].

A detailed airway examination should be performed from the nares to the distal bronchi to ensure there are no areas of obstruction that if treated may negate the need for a tracheostomy e.g. subglottic cysts or posterior glottis synechiae [7,10]. Other potential surgical interventions should be considered where appropriate e.g. epiglottoplasty for laryngomalacia.

2.3. Co-morbidities

Increasingly, tracheostomies are performed in children with multiple complex medical problems. Determining appropriate candidates for tracheostomy placement is often challenging. In some complicated cases, the risks of the procedure include cardiac arrest and death [19,20]. In a study by Watters et al., 62% of children had a complex chronic medical condition, 43% had ≥ 3 chronic conditions and 29% had other medical technology needs in addition to their tracheostomy [21]. A systematic review on the use of tracheostomy in pediatric obstructive sleep apnea (OSA) did not identify any mild or moderate case of OSA requiring tracheostomy without significant co-morbidities or syndromes e.g. cerebral palsy, neuromuscular disease and craniofacial abnormalities [17,22–24]. This was likely because most cases of OSA in children without co-morbidities can be managed with traditional interventions such as adenotonsillectomy [22]. Strang et al. reported that the presence of congenital heart disease was associated with increased mortality rates in infants who were ≤ 12 months old at time of tracheostomy [23].

Oral communication and feeding with a tracheostomy become more of a challenge in children with pre-existing neurological conditions [7]. Caregivers and families should be counselled on what potential changes this could pose for the child. Infants with severe cognitive deficits also deserve special consideration by the clinical team. The decision to provide chronic invasive ventilation in this group often raises ethical discussions within medical teams with some perceiving this a futile use of resources or prolonging the suffering of the child [18]. Clinicians must address their ethical obligations to each individual child and their family with patience, foresight and teamwork [18]. Understanding the values and goals of the family is critical in the decision-making process. Involving clinicians who care for children with tracheostomies and/or home ventilators in the discussion can be helpful. Additionally, facilitating the family access to other families whom have had positive as well as challenging experiences may assist with the decision-making process [25].

2.4. Caregiver education

The education needs of the caregivers should be reviewed frequently including prior to tracheostomy insertion, during the hospital stay and at discharge [26]. Due to the significant medical burden of a tracheostomy and long term mechanical ventilation, the psychological impact on the child and their family can weigh heavily [27,28]. Anticipatory guidance on long term considerations and potential complications during the informed consent discussion prior to tracheostomy insertion, is of paramount importance [7,27]. However, it is often difficult to counsel families on what to expect and the hardships involved [3,21]. Home-care teaching should begin before tracheostomy insertion to provide some insight for caregivers [29]. This should be individualized to the cultural needs of the family and conveyed at an unhurried pace. Education should include clinical decision-making skills including identifying and treating tracheostomy complications as well as technical skills of routine tracheostomy care [7,29]. Caregivers should be assessed for competencies in these skills in the hospital prior

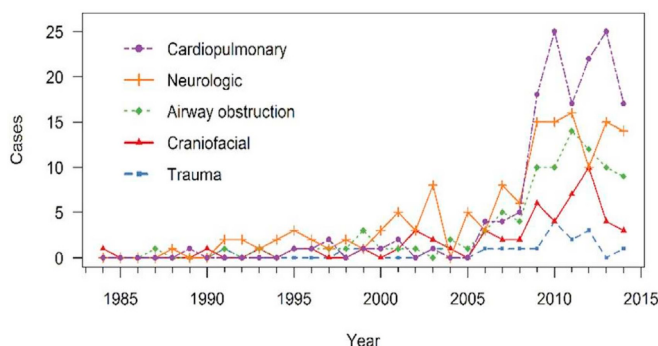


Fig. 1. Distribution of pediatric tracheostomy indications by year. (Reprinted from Int J Pediatr Otorhinolaryngol, 2016; 87:144-7. Gergin O, Adil EA, Kawai K, Watters K, Moritz E, Rahbar R. Indications of pediatric tracheostomy over the last 30 years: Has anything changed? Pages 144-7, Copyright 2016, with permission from Elsevier).

to discharge [26]. Any limitations or difficulties should be identified and addressed as appropriate. Hettige et al. demonstrated that the expectation, knowledge and confidence in delivering this type of care can remain a challenge for parents [30].

2.5. Economic considerations

Tracheostomies come at a high economic cost to the family and healthcare system when one considers both the initial hospitalization and tube placement and more so the post-operative care, which in children is 24-h care. Children with tracheostomies require skilled nursing care and this is particularly important during the initial period upon discharge home. The duration and extent of supplemental specialized home-care required should be decided by the tertiary care team on an individual basis with periodic reassessment [29]. In the absence of clear scientific evidence, financial issues including local and national insurance coverage may influence the home-care packages available to patients and families [31]. Health care teams must be familiar with local policies to develop care strategies that remain within these constraints but in the best interests of the patient [31].

2.6. Type of tracheostomy tube

Identifying the appropriate size (diameter and length) of a tracheostomy tube is paramount to the overall success of this intervention. Ideally the smallest diameter tube capable of providing adequate air exchange should be used to avoid tracheal mucosal injury [3,26]. At times a larger tube may be indicated in ventilated patients to prevent a significant air leak. A tube which is too long may cause obstruction or migrate into the right main bronchus leading to left lung collapse.

In general, uncuffed tracheostomy tubes are preferred over cuffed tracheostomy tubes in the pediatric population. Uncuffed tubes will avoid excessive mucosal injury potentially induced by the cuff and facilitate phonation around the tracheostomy tube. Sometimes, cuffed tracheostomy tubes are indicated in patients requiring ventilation with high pressures, nocturnal ventilation only (speaking around the deflated cuffed tracheostomy tube during the day) and patients with chronic translaryngeal penetration [29]. Custom tracheostomy tubes are also available and are used increasingly in the patient population with complex upper airway, tracheoesophageal and craniofacial anomalies. There are no specific recommendations on the optimal tracheostomy type for specific patient populations and hence physician and institutional preferences often play a major role in tracheostomy tube selection [31].

3. Post tracheostomy care

Pediatric tracheostomy placement is associated with a relatively high morbidity and mortality and every endeavour should be made to ensure optimal medical care and development of the child [4,32]. Post-operative care is often individualized to the patient's needs and physician's preference as there is limited data on the optimal frequency of routine surveillance and tube changes, home monitoring and speaking valve use.

3.1. Tracheostomy surveillance

After initial tracheostomy placement, the patient should be closely monitored in an ICU, often until the initial tube change. Stomal maturation is usually complete within 3–7 days and the first tube change generally occurs at this stage [26].

There are no clear guidelines regarding the ideal frequency of tracheostomy tube changes after the initial tube change. It is often driven by local practice and can range from daily to monthly [31]. Advantages of frequent tracheostomy tube changes include ensuring continued caregiver comfort with tube changes, whilst also possibly reducing the

risk of infection and tube occlusion due to inspissated secretions. However, frequent tracheostomy changes can also lead to stomal stretch and damage [29]. The American Thoracic Society (ATS) guidelines on tracheostomy care did not reach consensus on optimal frequency of tracheostomy change [29].

Post tracheostomy surveillance with endoscopy differs amongst centers, but in general is dependent on the indication for initial tracheostomy, in addition to the age of the child. For patients with rapidly evolving airway lesions, tracheoscopy with or without intervention e.g., tissue excision or dilation, may be required as often as every 2 weeks. Young infants who are growing rapidly may require tracheoscopy every 2–3 months to assess appropriate tube size, in contrast to teenage patients who may only require annual endoscopies. Most institutions also perform a formal airway evaluation prior to decannulation [33].

3.2. Humidification and suctioning

Humidification and suctioning are required to reduce the risk of tube obstruction, crusting and mucus plugs, as the normal functions of the upper respiratory tract have been bypassed by the tracheostomy. Various devices exist which assist in humidification including ventilators with built in humidifiers, saline nebulizers, saline drops and heat moisture exchangers (HME) often referred to as “Swedish or artificial noses”. These are filter devices in which moisture and heat are deposited during exhalation and returned during inhalation. HMEs can increase the work of breathing by increasing airway resistance and dead space and are not tolerated by all patients [34]. Patients may also have difficulty clearing secretions with a HME in situ and those with a large secretion burden may not tolerate it. A tracheostomy collar may be used in patients who do not tolerate a HME. Aerosol tubing is connected to a collar mask with the other end of the tubing attached to a nebulizer bottle and air compressor. Oxygen if required can be delivered through both a HME and tracheostomy collar.

Endotracheal suctioning to ensure airway patency and manage secretions is one of the most common procedures performed in patients with artificial airways [31,35]. There are two methods of endotracheal suctioning: open and closed. The open method requires a patient to be disconnected from a ventilator, whilst the closed method involves attachment of a sterile, closed in-line suction catheter to the ventilator circuit allowing the patient to stay connected to the ventilator throughout [35]. The depth at which to insert the suction catheter is of upmost importance to avoid tracheal epithelia damage and therefore the use of pre-marked catheters is strongly recommended [29]. The ATS consensus document on tracheostomy care states that suctioning should be performed on the basis of clinical assessment rather than specific time intervals, though a minimum of twice daily suctioning is recommended to ensure airway patency [29].

3.3. Speaking valves

One way speaking valves have proven successful in the adult population to enable patients to vocalize after tracheostomy tube placement. To promote the success of speaking valves in the adult population various criteria are recommended including tracheostomy tube size less than two-thirds of the tracheal lumen, medical stability, tolerance of having the tracheostomy tube cuff deflated and an ability to control secretions [29]. Unfortunately, there is a dearth of research on the use and benefit of speaking valves in the pediatric population. Most pediatric studies focus on tolerance of speaking valves rather than the impact on verbal communication [36]. Speaking valve trials are often started for a brief period e.g., 10 min under direct observation and gradually increased. As communication is an integral part of pediatric development more research is required in this area [36]. The ATS recommend that all patients regardless of diagnosis, age or expected duration of tracheostomy be referred to speech and language teams for assessment and appropriate follow-up [26,29].

Table 1
Perioperative complications of tracheostomy insertion.

Intraoperative	Early post-operative	Late post-operative
Hemorrhage	Hemorrhage	Granuloma formation
Air dissection	Tracheostomy malposition	Suprastomal collapse (tracheal ring compression, weakening and displacement)
Trauma to surrounding tissue	Tracheostomy obstruction	
Tracheostomy malposition	Wound infection	Tracheoesophageal fistula
Tracheostomy obstruction	Dysphagia	Tracheal & subglottic stenosis
Post obstructive pulmonary edema	Accidental decannulation	Tracheo-innominate artery fistula

3.4. Monitoring

The goal of home monitoring devices for children requiring chronic invasive mechanical ventilation is to provide early warning of any airway compromise. Options include pulse oximeters, end-tidal carbon dioxide monitors and apnea monitors, however, standards of care are lacking on both the type and frequency of such monitoring. The ATS suggests factors to be considered by the medical team when deliberating what type of home monitoring to use including patient age, tracheostomy size, degree of airway obstruction, underlying pathology, other medical conditions present, social environment and the behavior of the child [29].

Once prescribed by the medical team, home monitors should be reliable and maintained by the home care company. Appropriate training should be provided for families and caregivers. Ideally the monitors chosen should have a backup battery for portability in case of an emergency. Clinicians also find it useful to employ monitors with remote download capabilities facilitating medical assessment both in clinic and from the home.

Most portable ventilators also have monitoring and alarm capabilities to detect high or low pressure, apnea, high or low minute ventilation, low battery or power failure. Many ventilators can be equipped with a downloadable smart card to help the physician identify issues such as ventilator dyssynchrony, air leaks or inappropriate ventilator settings. Kun et al. described how the high tube resistance in small uncuffed tracheostomy tubes may prevent low pressure alarms from detecting accidental decannulation [37]. Low pressure and low minute ventilation alarms should be set appropriately to help detect ventilator leaks in children with smaller tracheostomy tubes along with additional monitoring e.g. pulse oximetry. Physicians may choose a combination of patient monitoring devices in the home to minimize the risk of a single monitor failing unpredictably e.g. pulse oximetry and ventilator alarms.

3.5. Inhaled medications

There is a paucity of recommendations regarding specific aerosol devices and techniques to use when administering inhaled medications via tracheostomy and the choice is often patient, physician and institution dependent. Differences in devices and techniques can result in a variable amount of drug delivered. A review by Berlinski concluded that aerosol delivery through pediatric tracheostomy tubes is impaired by small internal diameters and breathing patterns with low tidal volumes [38]. However, adult data comparing drug delivery between endotracheal tubes and tracheostomy tubes has shown that the latter delivers 50% more drug than the former due to the shorter length of the tracheostomy tube [39].

Vibrating mesh nebulizers are more efficient than jet nebulizers but are also more expensive [38]. Either device can be used with a tracheostomy however, high bias flows should be avoided as they can reduce aerosol delivery and interfere with ventilation [39,40]. Piccuito and Hess demonstrated that turning off high-flow oxygen before administration of aerosolized drugs to patients with tracheostomies via a jet nebulizer resulted in an increase in drug delivery of up to 3-fold [39].

In patients with tracheostomies who tolerate disconnection from a ventilator, pressurized metered-dose inhalers (pMDI) can be used to administer medications using a holding chamber designed for use with tracheostomies. However, if the patient cannot tolerate ventilator disconnection then the timing of the actuation is crucial. Failure to synchronize the pMDI actuation with an inhalation reduces aerosol delivery by 35% [38].

The use of assisted technique to administer aerosols either by nebulizer or pMDI varies amongst institutions [41]. Some reports suggest that assisted technique decreases lung delivery of pMDIs but results in increased tracheal deposition when nebulizers are used [40,41]. Berlinski and Chavez reported that the use of assisted technique with pMDI administration via tracheostomy resulted in a reduction in drug delivery ranging from 18 to 54% [40]. The difference between pMDIs and nebulizers regarding the effect of assistance on aerosol deposition could in part be explained by the continuous flow which a nebulizer provides.

4. Complications

Tracheostomy is a lifesaving operation for many however, it is also associated with potential serious complications. Nageswaren et al. highlighted the importance of discussion of both the positive and negative aspects of tracheostomy with families prior to tracheostomy placement including potential complications [27]. Mortality rates with pediatric tracheostomy are higher than the adult population, with highest rates in children receiving a tracheostomy under 1 year of age [32].

Medical teams must be vigilant for complications of tracheostomies which can be classified temporally as occurring intraoperatively, in the early post-operative period (first 7 days) and in the late post-operative period (after 7 days or after the first tracheostomy tube change) [7] (Table 1).

Fifty percent of deaths in tracheostomy patients are, however, due to progression of the patient's underlying disease rather than a complication of the tracheostomy [46]. In an emergency situation, carers and medical staff should be wary of complications related to both the tracheostomy itself and invasive mechanical ventilation but also cognizant of potential complications of the child's primary medical or surgical condition.

5. Decannulation

Decannulation is often the ultimate shared goal for the patient, their family and their multidisciplinary team [31]. Reported rates for successful decannulation in the pediatric population vary, ranging from 29 to 98% and are hugely impacted by the patient population in each case series reported [32]. Most recent studies show a successful decannulation rate of 29–37% [13,20]. Decannulation rates are higher in patients without neurological impairment [42].

Decannulation failure is defined as the need to replace the tracheostomy tube after decannulation. The incidence of decannulation failure varies from 9 to 45%, partially due to the lack of consensus on the length of time considered for failure determination with some studies reporting days and others months [43]. Various risk factors leading

Table 2
Risk factors for decannulation failure.

Physical risk factors	Functional risk factors
Granulomas	Insufficient deglutition reflexes
Tissue overgrowth	Suboptimal secretion management
Sub/Supraglottic stenosis	Intermittent apnea
Tracheomalacia	

to decannulation failure have been identified, which can be broadly divided into physical and functional categories (Table 2).

Mitchell et al. recommend that no mechanical ventilation support should be required for 2–4 months prior to decannulation [26]. Additionally, there should be no signs or symptoms of ongoing aspiration that would preclude decannulation [26].

5.1. Tracheostomy downsizing and capping trials

Most decannulation protocols begin with downsizing the tracheostomy to promote gradual closure of the stoma and to train the patient to breathe around the tracheostomy [10]. A trial of daytime capping is typically performed under direct observation, to ensure tolerance. If tolerated, the patient is then usually admitted overnight for a 24-h capping trial. If successful, the tracheostomy tube is removed and the stoma is occluded with an occlusive dressing to promote closure. Primary closure is not advised, due to the increased risk of infection and wound dehiscence [10].

The procedure of capping and tracheostomy downsizing is not universally employed in the decannulation process, due to concern for increased risk of mucus plugging and decreasing the cross-sectional area of the trachea to the degree that those who do not tolerate capping may still actually tolerate decannulation [33]. However, other authors contend that reduction and occlusion of the tube diameter can predict success of decannulation in addition to acclimatizing the child to changing airway physiology [44].

5.2. Polysomnogram

The role of polysomnography in decannulation protocols remains debatable, as many patients with mild or moderate OSA may still progress to successful decannulation. Gurbani et al. demonstrated the superiority of combining a polysomnogram and bronchoscopy to determine eligibility for decannulation [45]. Similar reports from Tunkel et al. and Robinson et al., highlighted the benefits of polysomnography in determining the appropriateness of decannulation [46,47]. Unfortunately, these studies are resource intensive and frequently not available for inclusion in decannulation protocols [33].

5.3. Bronchoscopy

Most institutions agree that a formal airway evaluation is essential prior to decannulation to ensure that there are no airway lesions that may prevent a safe decannulation such as vocal cord insufficiency, stomal granulation, suprastomal collapse, distal tracheal granulation or airway malacia [3,10]. Bronchoscopy is one of the most undisputed components of decannulation protocols as it not only provides diagnostic evaluation but also the opportunity for therapeutic airway treatments [33]. The importance of spontaneous breathing during bronchoscopy has been emphasized in many studies, to identify any dynamic collapse or obstruction [48].

6. Conclusions

Increasing numbers of neonates are surviving with complex medical conditions involving airway obstruction and/or cardiopulmonary

disease. Improvements in available technology and home-care resources allow greater numbers of these pediatric patients requiring chronic invasive ventilation to be cared for in the home. Medical practitioners caring for patients requiring long term tracheostomy placement face many challenging decisions often with limited or no clinical consensus guidance available. The success of chronic invasive ventilation in pediatric patients is determined by the capacity of the medical teams involved to ensure patient safety (e.g., appropriate home monitoring, adequate care giver education) and patient comfort (e.g., humidification, speech and swallow support).

Practice points

- Decisions regarding tracheostomy placement must be carefully considered by medical teams including assessment of the underlying medical condition as well as the psychological, social and economic impact on the patient and their family.
- Once a child is successfully discharged home on chronic invasive ventilation, there must be regular contact with the clinical teams involved to maintain high-quality tracheostomy care e.g., appropriate management of humidification, suction, inhaled medications and speaking valves.
- Decannulation practices vary between institutions but bronchoscopy, tracheostomy downsizing and capping trials are common. Polysomnography is useful but not always readily available.

Research directions

- Optimal timing of infant and pediatric tracheostomy insertion, particularly in the BPD population.
- Decannulation strategies for pediatric patients.
- Device development for the administration of aerosolized medications in children requiring tracheostomies with or without mechanical ventilation.
- Home monitoring protocols for pediatric patients requiring chronic invasive ventilation.

Declaration of competing interest

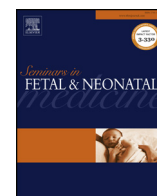
Frances Flanagan has no conflicts of interest and no funding sources.

Fiona Healy has no relevant conflict of interest or funding sources to declare.

References

- [1] Lewis CW, Carron JD, Perkins JA, Sie KC, Feudtner C. Tracheostomy in pediatric patients: a national perspective. *Arch Otolaryngol Head Neck Surg* 2003;129(5):523–9.
- [2] Gergin O, Adil EA, Kawai K, Watters K, Moritz E, Rahbar R. Indications of pediatric tracheostomy over the last 30 years: has anything changed? *Int J Pediatr Otorhinolaryngol* 2016;87:144–7.
- [3] Watters KF. Tracheostomy in infant and children. *Respir Care* 2017;62(6):799–825.
- [4] Alladi A, Rao S, Das K, Charles AR, D'Cruz AJ. Pediatric tracheostomy: a 13-year experience. *Pediatr Surg Int* 2004;20(9):695–8.
- [5] Adly A, Youssef TA, El-Begermy MM, Younis HM. Timing of tracheostomy in patients with prolonged endotracheal intubation: a systematic review. *Eur Arch Oto-Rhino-Laryngol* 2018;275(3):679–90.
- [6] Lee JH, Koo CH, Lee SY, Kim EH, Song IK, Kim HS, et al. Effect of early vs. late tracheostomy on clinical outcomes in critically ill pediatric patients. *Acta Anaesthesiol Scand* 2016;60(9):1281–8.
- [7] Deutsch E. Tracheostomy: pediatric considerations. *Respir Care* 2010;55(8):1082–90.
- [8] Luo J, Shepard S, Nilan K, Wood A, Monk HM, Jensen EA, et al. Improved growth and developmental activity post tracheostomy in preterm infants with severe BPD. *Pediatr Pulmonol* 2018;53(9):1237–44.
- [9] Funamura JL, Durbin-Johnson B, Tollefson TT, Harrison J, Senders CW. Pediatric tracheostomy: indications and decannulation outcomes. *The Laryngoscope* 2014;124(8):1952–8.

- [10] Campisi P, Forte V. Pediatric tracheostomy. *Semin Pediatr Surg* 2016;25(3):191–5.
- [11] Berry JG, Graham RJ, Roberson DW, Rhein L, Graham DA, Zhou J, et al. Patient characteristics associated with in-hospital mortality in children following tracheostomy. *Arch Dis Child* 2010;95(9):703–10.
- [12] Zhu H, Das P, Roberson DW, Jang J, Skinner ML, Paine M, et al. Hospitalizations in children with preexisting tracheostomy: a national perspective. *The Laryngoscope* 2015;125(2):462–8.
- [13] Douglas CM, Poole-Cowley J, Morrissey S, Kubba H, Clement WA, Wynne D. Paediatric tracheostomy-An 11 year experience at a Scottish paediatric tertiary referral centre. *Int J Pediatr Otorhinolaryngol* 2015;79(10):1673–6.
- [14] Sisk EA, Kim TB, Schumacher R, Dechert R, Driver L, Ramsey AM, et al. Tracheostomy in very low birth weight neonates: indications and outcomes. *The Laryngoscope* 2006;116:928–33.
- [15] Schmidt B, Asztalos EV, Roberts RS, Robertson CMT, Sauve RS, Whitfield MF. Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months: results from the trial of indomethacin prophylaxis in preterms. *JAMA* 2003;289:1124–9.
- [16] Walsh MC, Morris BH, Wraga LA, Vohr BR, Poole WK, Tyson JE, et al. Extremely low birthweight neonates with protracted ventilation: mortality and 18-month neurodevelopment outcomes. *J Pediatr* 2005;146:798–804.
- [17] Bannink N, Nout E, Wolvius EB, Hoeve HLJ, Joosten KFM, Mathijssen IMJ. Obstructive sleep apnea in children with syndromic craniosynostosis: long-term respiratory outcome of midface advancement. *Int J Oral Maxillofac Surg* 2010;39(2):115–21.
- [18] Robinson WM. Ethical considerations in chronic invasive mechanical ventilation in pediatrics. In: Sterni LM, Carroll JL, editors. *Caring for the ventilator dependant child: a clinical guide*. Humana Press; 2016. p. 57–69.
- [19] Mahadevan M, Barber C, Salkeld L, Douglas G, Mills N. Pediatric tracheostomy: 17 year review. *Int J Pediatr Otorhinolaryngol* 2007;71(12):1829–35.
- [20] Carr MM, Poje CR, Kingston L, Kielma D, Heard C. Complications in pediatric tracheostomies. *The Laryngoscope* 2001;111(11):1925–8.
- [21] Watters K, O'Neill M, Zhu H, Graham RJ, Hall M, Berry J. Two-year mortality, complications, and healthcare use in children with medicaid following tracheostomy. *The Laryngoscope* 2016;126(11):2611–7.
- [22] Fray S, Biello A, Kwan J, Kram YA, Lu K, Camacho M. Tracheostomy for paediatric obstructive sleep apnoea: a systematic review. *J Laryngol Otol* 2018;132:680–4.
- [23] Strang AR, Briddell JW, Barth PC, Shah UK, Chidekel A. Risk factor analysis for mortality among infants requiring tracheostomy. *Pediatr Pulmonol* 2018;53(8):1115–21.
- [24] Rizzi CJ, Amin JD, Isaiiah A, Valdez TA, Jeyakumar A, Smart SE, et al. Tracheostomy for severe pediatric obstructive sleep apnea: indications and outcomes. *Otolaryngol Head Neck Surg* 2017;157:309–13.
- [25] Wilfond BS. Tracheostomies and assisted ventilation in children with profound disabilities: navigating family and professional values. *Pediatrics* 2014;133(Supplement):S44–9.
- [26] Mitchell RB, Hussey HM, Setzen G, Jacobs IN, Nussenbaum B, Dawson C, et al. Clinical consensus statement: tracheostomy care. *Otolaryngol Head Neck Surg (U S)* 2013;148(1):6–20.
- [27] Nageswaran S, Golden SL, Gower WA, King NMP. Caregiver perceptions about their decision to pursue tracheostomy for children with medical complexity. *J Pediatr* 2018;203:354–60.
- [28] Harnick CJ, Bissell C, Parsons SK. The impact of paediatric tracheostomy on parental caregiver burden and health status. *Arch Otolaryngol Head Neck Surg* 2003;129:1065–9.
- [29] ATS. American Thoracic Society care of the child with a chronic tracheostomy. *Crit Care Med* 1999;161(1):297–308.
- [30] Hettige R, Arora A, Ifecho S, Narula A. Improving tracheostomy management through design, implementation and prospective care bundle; how we do it. *Clin Otolaryngol* 2008;33:474–94.
- [31] Lewarski JS. Long-term care of the patient with a tracheostomy. *Respir Care* 2005;50(4):534–7.
- [32] Zenk J, Fyrmpas G, Zimmermann T, Koch M, Constantinidis J, Iro H. Tracheostomy in young patients: indications and long-term outcome. *Eur Arch Oto-Rhino-Laryngol* 2009;266(5):705–11.
- [33] Wirtz N, Tibesar RJ, Lander T, Sidman J. A pediatric decannulation protocol: outcomes of a 10-year experience. *Otolaryngol Head Neck Surg (U S)* 2016;154(4):731–4.
- [34] Tweedie DJ, Cooke J, Stephenson KA, Gupta SL, Pepper CM, Elloy MD, et al. Paediatric tracheostomy tubes: recent developments and our current practice. *J Laryngol Otol* 2018;132(11):961–8.
- [35] Restrepo RD, Brown JM, Hughes JM. AARC Clinical Practice Guidelines. Endotracheal suctioning of mechanically ventilated patients with artificial airways 2010. *Respir Care* 2010;55(6):758–64.
- [36] Zabih W, Holler T, Syed F, Russell L, Allegro J, Amin R. The use of speaking valves in children with tracheostomy tubes: what is the scope of the literature? *Respir Care* 2017;62(12):1594–601.
- [37] Kun SS, Nakamura CT, Ripka JF, Davidson Ward SL, Keens TG. Home ventilator low-pressure alarms fail to detect accidental decannulation with pediatric tracheostomy tubes. *Chest* 2001;119(2):562–4.
- [38] Berlinski A. Pediatric aerosol therapy. *Respir Care* 2017;62(6):662–77.
- [39] Piccuito CM, Hess DR. Albuterol delivery via tracheostomy tube. *Respir Care* 2005;50(8):1071–6.
- [40] Berlinski A, Chavez A. Albuterol delivery via metered dose inhaler in a spontaneously breathing pediatric tracheostomy model. *Pediatr Pulmonol* 2012;48(10):1026–34.
- [41] Corbett HJ, Mann KS, Mitra I, Jesudason EC, Losty PD, Clarke RW. Tracheostomy- a 10 year experience from a UK pediatric surgical center. *J Pediatr Surg* 2007;42(7):1251–4.
- [42] Tsuboi N, Ide K, Nishimura N, Nakagawa S, Morimoto N. Pediatric tracheostomy: survival and long-term outcomes. *Int J Pediatr Otorhinolaryngol* 2016;89:81–5.
- [43] Pozzi M, Galbiati S, Locatelli F, Clementi E, Strazzer S. Performance of a tracheostomy removal protocol for pediatric patients in rehabilitation after acquired brain injury: factors associated with timing and possibility of decannulation. *Pediatr Pulmonol* 2017;52(11):1509–17.
- [44] Kubba H, Cooke J, Hartley B. Can we develop a protocol for the safe decannulation of tracheostomies in children less than 18 months old? *Int J Pediatr Otorhinolaryngol* 2004;68(7):935–7.
- [45] Gurbani N, Promyothin U, Rutter M, Fenchel MC, Szczesniak RD, Simakajornboon N. Using polysomnography and airway evaluation to predict successful decannulation in children. *Otolaryngol Head Neck Surg (U S)* 2015;153(4):649–55.
- [46] Tunkel D, McColey SA, Baroody FM, Marcus CL, Carroll JL, Loughlin GM. Polysomnogram in the evaluation of readiness for decannulation in children. *Arch Otolaryngol Head Neck Surg* 1996;122:721–4.
- [47] Robison JG, Thottam PJ, Greenberg LL, Maguire RC, Simons JP, Mehta DK. Role of polysomnography in the development of an algorithm for planning tracheostomy decannulation. *Otolaryngol Head Neck Surg (U S)* 2015;152(1):180–4.
- [48] Gray RF, Todd NW, Jacobs IN. Tracheostomy decannulation in children: approaches and techniques. *The Laryngoscope* 1998;108(1):8–12.



Long term outcomes in chronic lung disease requiring tracheostomy and chronic mechanical ventilation

Georgia Koltsida^{a,*}, Sofia Konstantinopoulou^b

^a First Department of Pediatrics, National and Kapodistrian University of Athens, School of Medicine, Aghia Sophia Children's Hospital, Greece

^b Division of Pulmonary Medicine, Department of Pediatrics, Sheikh Khalifa Medical City, Al Karama Street, Tibbiyya, Abu Dhabi, United Arab Emirates

ARTICLE INFO

Keywords:

Bronchopulmonary dysplasia
Tracheostomy
Chronic mechanical ventilation
Respiratory outcomes
Pulmonary function
Exercise testing
Neurodevelopmental outcomes
Systemic corticosteroids

ABSTRACT

Bronchopulmonary dysplasia (BPD) is the most common serious complication associated with preterm birth. Infants with severe BPD often require prolonged and intensive pulmonary care. Among those with the most severe lung disease, this care may include tracheostomy and long-term invasive mechanical ventilation. Although there is a plethora of data on long term respiratory and developmental outcomes of BPD survivors, relevant information on BPD survivors requiring chronic respiratory failure are limited. When compared to those born at term gestation, infants with BPD requiring chronic ventilation are at increased risk of hospitalizations and develop more frequent lower respiratory infections. In childhood and young adulthood, spirometry often shows an obstructive flow pattern. From a neurodevelopmental standpoint, the short-term outcomes appear optimistic, with improvement in growth and increased participation in development-promoting activities. Nonetheless, children born prematurely are vulnerable for long term cognitive, educational and behavioral impairments. BPD is an additional risk factor which exacerbates these deficits, thus contributing to lifelong neurodevelopmental impairments of prematurity.

1. Introduction

Bronchopulmonary dysplasia (BPD) is one of the most significant and serious complications of prematurity. It is estimated to affect 25% of newborns with a birth weight under 1000 gr, and 70% of those born between 22 and 26 weeks of gestation [1]. Despite paramount advances in the management of BPD such as administration of antenatal corticosteroids, surfactant replacement and effective modes of invasive and noninvasive ventilatory support, the prevalence of BPD has plateaued over the past decades.

BPD was originally described as the respiratory condition affecting preterm infants typically born at or after 32 weeks exposed to aggressive ventilation and high concentrations of inspired oxygen [2]. However, the term 'new BPD' has been established, and is characterized mainly by alveolar simplification and abnormal pulmonary vascularization [2]. The current BPD definition as proposed by the National Institute of Child Health and Human Development (NICHD), includes the treatment with supplemental oxygen for at least 28 days, and categorizes its severity into mild, moderate and severe according to the level of respiratory support required near to term. Infants with severe BPD requiring positive pressure ventilation at 36 weeks' postmenstrual age are more likely to transition into prolonged mechanical ventilation

via tracheostomy while in the neonatal intensive care unit. While the exact prevalence of children with severe BPD necessitating positive pressure ventilation at home is unknown, it is estimated that the number of patients with BPD requiring tracheostomy and prolonged mechanical ventilation has been increasing significantly from 0.7 to 2 per 100.000 to 6.3 per 100.000 children, over the past decades [3–5].

Most tracheostomies in children are performed in infants less than 12 months of age [6]. In addition to the need for prolonged mechanical ventilation, other indications include significant airway abnormalities such as severe tracheomalacia, bronchomalacia, and subglottic stenosis. The optimal timing of tracheostomy placement is unknown. Studies have shown that early tracheostomy placement reduces the risk of subglottic stenosis, decreases the need for sedation, improves comfort and most importantly, promotes cognitive and physical growth by facilitating the transition to homecare [5,7].

Both the presence and severity of BPD are independently associated with cognitive impairment [8,9]. Although there are emerging data on long term pulmonary and neurodevelopmental outcomes in infants with BPD, there is limited information on the subgroup of patients who require prolonged mechanical ventilation. Our aim is to review the literature and provide data on the respiratory and neurodevelopmental outcomes in children with severe BPD who are supported by long term

* Corresponding author.

E-mail addresses: gkoltsida@hotmail.com (G. Koltsida), SKonstantinopoulou@seha.ae (S. Konstantinopoulou).

<https://doi.org/10.1016/j.siny.2019.101044>

mechanical ventilation through tracheostomy.

2. Respiratory outcomes

2.1. Rehospitalization

Hospital readmission rates for respiratory illness in children with BPD range between 43% up to 63% during the first 2 years of life [10–12]. Hospitalization rates for BPD infants are not only higher than those of the general population, but are also higher than those of very low birth weight infants without lung disease [10,12]. The most common causes for rehospitalization in this population are respiratory diseases including reactive airway disease, pneumonia and respiratory syncytial virus infection, which account for 65% of readmissions in the first year, and 81% in the second year.

The severity of BPD has been associated with longer hospitalization, but there are limited data specifically regarding ventilator-dependent patients. A retrospective cohort study by Kun et al. [13] on newly discharged pediatric patients on home mechanical ventilation, reported a 40% 12-month incidence of non-elective hospitalizations, with close to half of these hospitalizations occurring during the first 3 months after their initial discharge. Pneumonia and tracheitis were the most common causes of readmission. In another retrospective cohort study conducted by Cristea [14] et al. which included 102 patients with severe BPD and ventilator dependence followed over the course of a total of 871 person-years, the readmission rate was impressive with a total number of 675 events. The incidence of rehospitalization was significantly higher before decannulation (554 vs. 121 events, $p < 0.0001$). The decrease in the patients' readmission rate after decannulation could be attributed to removal of tracheostomy, improvement of BPD, or both. After 4–5 years of age, hospitalizations for respiratory problems tend to decrease [15,16]. Nonetheless, chronic respiratory symptoms continue to be reported in greater frequency among patients with BPD than those born at term without lung disease in most studies.

2.2. Asthma-like signs and symptoms

There have been numerous studies describing the increased incidence of asthma-like symptoms in BPD patients. In a systematic review and meta-analysis of preterm birth and childhood wheezing disorders, researchers identified 30 studies undertaken between 1995 and 2013 which is a time span chosen to allow for changes in the management of prematurity, and investigated the association between prematurity and asthma/wheezing in more than 1.5 million children. Preterm birth was associated with an increased risk of wheezing, and the risk was particularly high among children born very preterm (< 32 weeks gestational age). The population attributable risk of prematurity for childhood wheezing disorders was more than 3.1%, which means that if there were no premature births, then there would have been more than 3.1% of reduction in wheezing disorders in childhood [17]. While evidence shows that prematurity increases the risk of asthma, it has been emphasized that the pathogenesis of those symptoms may significantly differ.

In the EPICure study [18], a population based study including extremely premature infants, born between 22 and 26 weeks' gestational age, children born prematurely had significantly more chest deformities and respiratory symptoms at age 11 years compared to age-, sex-, ethnicity-matched peers. Specifically, twice as many had a diagnosis of asthma (25% vs. 13%, $p < 0.01$). In this study, three quarters of the cohort were described as moderate to severe BPD, but there were no technology dependent children included.

A study from a Danish collaborative group reported that of 508 19-year old adults born prematurely, those who had BPD had a higher prevalence of respiratory symptoms, and females were more likely to be affected than males [19]. Northway et al. [20], followed twenty six BPD

survivors with a mean age of 18.3 years, and reported that 25% of adolescents with BPD had significant pulmonary symptoms including higher number of wheezing episodes, pneumonias, and use of long-term medications, compared with age-matched controls who were also born prematurely but did not require mechanical ventilation, as well as compared to a group born at full term.

In summary, extreme prematurity is associated with increased respiratory morbidity which persists into middle childhood and young adulthood. This is particularly accentuated in patients with BPD.

2.3. Pulmonary function

It has been well described that children with BPD demonstrate an obstructive pattern of lung disease which is confirmed by functional respiratory tests [21,22]. Fakhoury et al., [23] studied forty-four children with moderate and severe BPD and mean gestational age of 25.6 weeks with serial measurements of lung function at 6, 12 and 24 months after initial discharge from the neonatal care unit. Their results showed that children with BPD had low partial expiratory airflow measured by V(max)FRC compared with normative data, with mean z score (+ or -SD) of -1.92 (+ or -1.04), -1.79 (+ or -1.5), and -1.67 (+ or -1.5) at 6, 12 and 24 months respectively. There was no significant improvement in z scores ($P = 0.66$), and 45% of the patients had a z score value of less than 2 SDs below the mean at the end of the study. In summary, children with mostly moderate to severe BPD continued to show significant abnormalities with airflow limitation based on lung function testing during the first 3 years of life.

In the EPICure cohort [24], the peak expiratory flow (PEF) measurements obtained in extremely preterm children at 6 years of age, were on average 39 l/min (95% CI 30 to 47) lower than in the comparison group. BPD was the only independent associate of PEF. In the same population study, the assessed respiratory function at 11 years in children with BPD showed an abnormally low baseline lung function; forced expiratory volume at 1 s FEV1, FEV1/FVC, and forced expiratory flow at 25–75% of vital capacity, FEF 25–75. There was a statistically significant increase in the FEV1 after administration of bronchodilators. Interestingly, other studies suggest that obstructive lung disease symptoms in BPD are less responsive to bronchodilators and inhaled corticosteroids which could be explained by an irreversible airflow limitation [25]. Doyle et al. [26], studied 33 BPD survivors who were born during 1977–1982 and had mean age of 18.9 years at the time of the pulmonary function testing. This study demonstrated significantly low ($< 75\%$) FEV1/FVC ratio in adults with BPD compared to controls as well as a gradual deterioration between 8 and 18 years.

While there is abundance of data on impaired pulmonary function in children and adolescents with history of BPD, limited information exists regarding the spirometric values in patients with severe BPD requiring chronic ventilatory support. In one study by Cristea et al. [27], 19 patients with severe BPD who were previously ventilator dependent at home underwent spirometry once they were able to follow commands. The median age of first reproducible spirometry measurement was 6.6 years, and the results showed evidence of severe airflow obstruction as reflected by z scores. More so, serial spirometric measurements' slopes revealed that the airway obstruction remained static over time.

Given that airway function tracks through life [28], those with reduced lung function in childhood are likely to retain this position through to adulthood and are thus likely to be among the first to reach a critical threshold for the onset of chronic obstructive pulmonary disease (COPD) with subsequent ageing. It appears that pulmonary function impairment in survivors of BPD who had chronic ventilation at home predisposes to a COPD phenotype later in life. This situation is likely to be exacerbated by the high prevalence of active smoking [29] and reduced exercise capacity which has been reported in ex-preterm adolescents and adults [30].

2.4. Exercise testing

There are several studies that have examined exercise capacity in BPD survivors and concerns have been raised about impaired physical activity persisting through adulthood [31]. The proposed mechanisms are exercise induced bronchoconstriction, decreased lean muscle mass and strength, compromised ventilatory response, and impaired lung function. In a longitudinal follow up study [18,32], 11 year old children born prior to 25 weeks' gestational age (71% with BPD) were matched with controls. Participants performed apart from spirometry, body plethysmography, gas transfer testing and a peak exercise testing on a cycle ergometer. The investigators concluded that children born extremely premature had lower z-scores in FEV1 and RV (residual volume), significant reduction in peak oxygen consumption and employed greater breathing frequencies and lower tidal volumes during exercise. However, no differences in physical activity were observed between the two groups. Unfortunately, there are no data on exercise capacity in children with BPD who were previously ventilatory dependent, or even stratified results based on severity of BPD.

2.5. Pulmonary arterial hypertension

Several factors may contribute to significant reduction in cross-sectional area of the pulmonary vascular bed, such as altered vascular development and vascular remodeling with smooth muscle cell proliferation. These give rise to an increase in pulmonary vascular resistance, which in turn leads to the onset of pulmonary arterial hypertension. This has often been associated with higher morbidity and mortality in BPD infants, especially in the first 6 months after the initial diagnosis [33]. This diagnosis is thus important not only for prognostic purposes but also to ensure appropriate treatment [34]. It is not currently known how long the pulmonary vascular effects of BPD persist into later life. Nonetheless, it is speculated that pulmonary vascular reactivity to hypoxia, and the negative effects of BPD on the global cardiac performance of both ventricles and on pulmonary arterial pressure may persist even into adulthood. Although technically difficult, future non-invasive studies could assess pulmonary vascular function in adolescent and/or adult survivors of preterm birth.

Liberation from mechanical ventilation and decannulation.

In infants with severe BPD, tracheostomy is generally considered if they are beyond 40 weeks postmenstrual age and anticipated to require high-level respiratory support (either invasive mechanical ventilation or high level non-invasive support) for a prolonged period of time. Often, this decision is driven by each institution's clinical practice and accounts for each patient's clinical status. As home assisted ventilation in children has evolved significantly over the last decade; hence more data are emerging on the outcome of pediatric patients with chronic respiratory failure and tracheostomy [5,7,35]. However, there is still limited information on the subgroup of BPD patients who require home ventilation.

Mandy et al. [36], reported a survival rate of 77% in 22 children who were placed on chronic mechanical ventilation due to BPD in a single institution. The causes of death were not always known in the aforementioned studies, but accidental decannulation and cardiopulmonary arrest were reported. In a single institution study by Com et al. [37], children with BPD without central nervous system insult were more likely to be decannulated within 5 years while in another center, the median age of decannulation was 38 months, almost 10 months after liberation from mechanical ventilation. Similarly, Cristea et al. [14] reviewed the medical charts of patients with severe BPD who were dependent on home mechanical ventilation and were enrolled over the course of 27 years. Of the evaluable 102 patients, 83 patients were alive with a survival rate of 81.4%. The median age at liberation from mechanical ventilation was 24 months (interquartile range, 19–33) and at decannulation was 37.5 months (interquartile range, 31.5–45), with a median interval between liberation from ventilation

and decannulation of 11 months. Although extreme prematurity associated with severe BPD necessitating mechanical ventilation carries significant risks of morbidity and mortality, successful liberation from mechanical ventilation is likely to occur. Future prospective cohort studies are needed in order to further elucidate this topic.

2.6. Prematurity and neurodevelopmental outcomes

During 24–40 weeks of gestation, multiple complex events critical for brain development take place, including axonal and subplate growth, differentiation of premyelinating oligodendrocytes, and proliferation and migration of gamma-aminobutyric acid-ergic neurons [38]. These processes are highly vulnerable to pathogenic factors, such as hemorrhagic events, hypoxic-ischemic events, and inflammation, and may be further exacerbated by environmental factors, such as stress and malnutrition [39]. Neuropathology associated with prematurity includes both direct brain injury of which white matter lesions are most common and secondary neuronal abnormalities affecting gray matter. These disturbances in brain development are reflected in reduced overall brain volume in childhood and adolescence, with reductions being evident in both gray and white matter [40]. White matter abnormalities in particular have been associated with neurocognitive deficits.

Specifically, Bhutta et al. showed the detrimental effect of preterm birth on intelligence based on cohorts of children born before 1990 [41]. Similar findings were published in the meta-analysis based on 27 studies including preterm children born between 1975 and 2000 [42]. A meta-analysis of 71 studies [43] which included 7752 extremely or very low preterm and 5155 full term children, showed a large 0.86 standard deviation difference in intelligence between extremely or very preterm children and controls which corresponds to 13 points in intelligence scores (IQ). A difference in intelligence of almost 1 SD is likely to have important consequences for academic achievement and socioeconomic outcomes. Furthermore, this difference was stable over age (5–20 years) and birth year (1990–2008). This implies that despite medical advances, overall improvement of neurodevelopmental outcomes over the years seems to be marginal, therefore emphasizing the need to focus on improving long-term cognitive outcomes of premature infants.

2.7. BPD and neurodevelopmental outcomes

Previous studies showed a positive association between BPD and brain anomalies in preterm infants [44], but the mechanisms remain to be elucidated. Specifically, Short et al. sought to examine the effects of BPD and very low birth weight (VLBW) on the cognitive and academic achievement of a large sample of 8 year old children [45]. The BPD group demonstrated deficits compared with the VLBW group and the term children in intelligence, mathematics, and gross motor skills, as well as in need for special education services. After controlling for birth weight, and neurologic problems, BPD and/or duration of supplemental oxygen therapy predicted lower performance IQ, perceptual organization, full scale IQ, motor and attention skills, as well as special educational placement. In a meta-analysis including 71 studies (7752 extremely or very low preterm and 5155 full term children), BPD accounted for 65% of the variance in intelligence across studies. One factor implicated in the pathogenesis of both BPD and brain injury in preterm infants is oxidative stress, which is defined as an imbalance between the generation of free radicals and antioxidant defense, and free iron release [46]. Organ immaturity, hypoxia-ischemia, hyperoxia, inadequate nutrition, and mechanical ventilation further increase the risk for free radical-induced injury [47]. Animal studies have shown that hyperoxia results in both lung and brain injury, and that the severity of lung injury is positively related to the severity of brain injury. Another plausible explanation is that children with BPD have reduced pulmonary function, increased airway resistance and reactivity, and

decreased exercise tolerance starting from preschool age, through early adolescence and into adulthood [45]. These respiratory problems may limit opportunities for these children to engage in the physical activities necessary to develop gross motor skills.

Finally, more BPD children may be enrolled in lower grades. This can be explained by several factors. Many parents of children with a history of BPD have indicated that they chose to delay school entry for a variety of reasons, including short stature, history of recurrent illness and hospitalizations, as well as perceptions of “increased vulnerability”. In addition, given the multiplicity of difficulties experienced by both the child and the family during the early years of life, educational specialists may have advocated for delayed entry into formal education. In summary, both the presence and the severity of BPD strongly influence neurodevelopmental outcomes and a protracted course of mechanical ventilation is associated with increased neurodevelopmental disability in this population [9].

2.8. Postnatal corticosteroids and neurodevelopmental outcomes

Postnatal corticosteroids were widely used in the past to treat BPD, while later evidence showed substantial adverse consequences for neurodevelopment. Changes in neonatal practice such as the largely decreased use of postnatal corticosteroids, may have resulted in some improvement in cerebral palsy and neurosensory disability rates [48]. While results of a recent meta-analysis did not suggest that the strong association between BPD and intelligence was mainly attributed to postnatal corticosteroid use [43], future studies are needed to further elucidate the mechanisms underlying the association between BPD and neurodevelopment, taking into account the postnatal use of corticosteroids. Furthermore, based on recent evidence it seems that hydrocortisone may affect neurocognitive development to a lesser extent than dexamethasone [49].

2.9. Tracheostomy and neurodevelopmental outcomes

Singer et al. reported developmental outcomes at an average of 5 years in a cohort of 130 infants from 2 hospitals who received tracheostomies before 13 months of age during 1972–1982 [50]. Twenty-nine percent died before follow up and 45% of survivors were classified with mental retardation or some form of neurological deficit. In a single-center study of 41 infants with tracheostomies 97% had abnormal muscle tone, 36% had cerebral palsy, and 24% required hearing aids at a mean age of 27 months. Among those evaluated after 12 months of age, 68% had significant developmental delays. In a questionnaire-based study of functional status in former very preterm infants with tracheostomies, parents reported deterioration over time, especially in the areas of responsiveness, activity, and interpersonal functioning [51]. In a retrospect cohort study [52] from 16 centers of the NICHD Neonatal Network over 10 years (2001–2011), infants who survived to at least 36 weeks (N = 8, 683), including 304 infants with tracheostomies were studied. Tracheostomies were associated with adverse neurodevelopmental outcomes. Death or neurodevelopmental impairment (NDI) occurred in 83% of infants with tracheostomies compared to 40% of those without. [(odds ratio (OR) adjusted for center 7.0 (95% CI 5.2–9.5)]. After adjustment for potential cofounders, odds of death or NDI remained higher [OR 3.3% (95%CI, 2.4–4.6)]. Although tracheostomy might itself put children at risk for poor outcomes, such a causal relationship is less likely than a non-causal association between tracheostomy and significantly increased risk for poor outcome. It is likely that tracheostomy is a marker for risk of an adverse outcome. Clinicians considering tracheostomy placement for an individual patient could use these data to help parents grasp potential long term outcomes.

Interestingly, death or NDI was lower in infants who received their tracheostomies, before, rather than after 120 days of life [adjusted OR 0.5 (95%CI, 0.3–0.9)]. These results suggest a possible association

between earlier (< 120 days) vs. later (> 120 days) tracheostomy placement and better neurodevelopmental outcomes. These results support the work of several authors who have suggested that in older children and adults, tracheostomy placement should be performed as soon as possible [5]. Some plausible explanations are that while an infant awaits a tracheostomy placement, the medical focus is often on strategies to enable weaning and limit ventilator-associated lung injury. Following a tracheostomy placement, the focus may then shift to maximizing parent-infant interaction and developmental enrichment. In addition, there is often opportunity to wean off sedating medications, which may be associated with increased risk of NDI, after tracheostomy placement. In a retrospective analysis of a cohort of infants born < 32 weeks gestation or birth weights < 1500 g with severe BPD who underwent tracheostomy placement between 2010 and 2016 in a quaternary referral newborn and infant intensive care unit, tracheostomy placement was associated with improved proportional growth and increased participation in activities promoting development skills acquisition and reduced daily sedation requirements in preterm infants with severe BPD [53]. More importantly, severity of illness, indication for tracheostomy, anesthetic exposure, or other factors may influence either the timing of tracheostomy or developmental outcomes, leading to potential bias. Further research is needed to address the question of optimal timing for tracheostomy placement, prior to confidently counseling parents toward earlier decisions about tracheostomy placement.

2.10. Future directions

Given the projected global increases in children surviving preterm birth, there are strong economic incentives for secondary prevention of disability associated with preterm birth. Preventive measures should include minimizing lung injury before and after delivery, long term surveillance and appropriate treatment through childhood in order to minimize the prenatal and postnatal factors that affect the immature lung. Having failed to reach their optimal peak lung function in early adulthood, there are concerns of accelerated lung function decline in BPD survivors. Even if the rate of decline in lung function is normal, the threshold for respiratory symptoms will be crossed early. As the management of these subjects in adulthood is largely evidence free, continued surveillance of young adults with a history of BPD will be critical to understand the long term impact of neonatal lung injury on pulmonary maturation and aging. There are a number of clinical and research priorities to maximize the quality of life and lung health in the longer term in understanding the underlying mechanisms and optimizing treatment, rather than extrapolating from other airway diseases.

BPD is found to be a crucial factor for long-term neurodevelopmental and cognitive outcomes above and beyond the effects of prematurity. Despite advancing neonatal health care, studies show no indication of significant improvements in long-term neurodevelopmental outcomes. This suggests that reducing the incidence of BPD in premature children would be beneficial. This suggests that reducing the incidence of BPD in premature children would be beneficial. To our knowledge, there is no single prevention or intervention strategy proven to have a considerable influence on the incidence of BPD. The fact that multiple factors seem to be involved in the development of BPD and neonatal brain injury advocates a multifactorial approach for prevention and treatment. Potential strategies may include an optimal ventilation strategy and oxygen concentration, anti-inflammatory agents, antioxidant therapy, and adequate nutritional support.

Moreover, research has shown that impairments in executive function for preterm survivors extend into adulthood with greater deficits found in adults with BPD including difficulties with planning, initiating new tasks and monitoring the outcome of behaviors. Such deficits affect the day to day lives of these individuals and have consequences in their social functioning, educational attainment and quality of life. These findings imply that, children with BPD should be thoroughly assessed to

identify cognitive impairments, and allow early intervention aiming at ameliorating their effects.

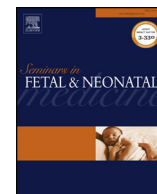
Finally, we need to acknowledge that although there are emerging studies on long term pulmonary and neurodevelopmental outcomes in BPD, there is very limited data regarding patients with severe BPD necessitating chronic ventilatory support. Future studies are needed in order for health care providers and families to better understand how chronic ventilation can impact the respiratory outcomes and the long term development of infants with severe BPD. This will help establish evidence based clinical guidelines and strengthen the multidisciplinary approach needed in caring for these vulnerable patients across their life span, in order to reach their full potential.

Declaration of competing interest

The authors have no conflicts of interest.

References

- [1] Ancel PY, Goffinet F, Group E-W, et al. Survival and morbidity of preterm children born at 22 through 34 weeks' gestation in France in 2011: results of the EPIPAGE-2 cohort study. *JAMA Pediatr* 2015;169(3):230–8.
- [2] Kalikkot Thekkevedu R, Guaman MC, Shivanna B. Bronchopulmonary dysplasia: a review of pathogenesis and pathophysiology. *Respir Med* 2017;132:170–7.
- [3] Amirnovin R, Aghamohammadi S, Riley C, Woo MS, Del Castillo S. Analysis of a pediatric home mechanical ventilator population. *Respir Care* 2018;63(5):558–64.
- [4] Simonds AK. Home ventilation. *Eur Respir J* 2003;22(Supplement 47):38s–46s.
- [5] Overman AE, Liu M, Kurachek SC, et al. Tracheostomy for infants requiring prolonged mechanical ventilation: 10 years' experience. *Pediatrics* 2013;131(5):e1491–1496.
- [6] Lewis CW, Carron JD, Perkins JA, Sie KC, Feudtner C. Tracheostomy in pediatric patients: a national perspective. *Arch Otolaryngol Head Neck Surg* 2003;129(5):523–9.
- [7] Wright MFA, Wallis C. Investigation and management of the long-term ventilated premature infant. *Early Hum Dev* 2018;126:10–7.
- [8] Natarajan G, Pappas A, Shankaran S, et al. Outcomes of extremely low birth weight infants with bronchopulmonary dysplasia: impact of the physiologic definition. *Early Hum Dev* 2012;88(7):509–15.
- [9] Walsh MC, Morris BH, Wraga LA, et al. Extremely low birthweight neonates with protracted ventilation: mortality and 18-month neurodevelopmental outcomes. *J Pediatr* 2005;146(6):798–804.
- [10] Chye JK, Gray PH. Rehospitalization and growth of infants with bronchopulmonary dysplasia: a matched control study. *J Paediatr Child Health* 1995;31(2):105–11.
- [11] Furman L, Baley J, Borawski-Clark E, Aucott S, Hack M. Hospitalization as a measure of morbidity among very low birth weight infants with chronic lung disease. *J Pediatr* 1996;128(4):447–52.
- [12] Gross SJ, Iannuzzi DM, Kveselis DA, Anbar RD. Effect of preterm birth on pulmonary function at school age: a prospective controlled study. *J Pediatr* 1998;133(2):188–92.
- [13] Kun SS, Edwards JD, Ward SL, Keens TG. Hospital readmissions for newly discharged pediatric home mechanical ventilation patients. *Pediatr Pulmonol* 2012;47(4):409–14.
- [14] Cristea AI, Carroll AE, Davis SD, Swigonski NL, Ackerman VL. Outcomes of children with severe bronchopulmonary dysplasia who were ventilator dependent at home. *Pediatrics* 2013;132(3):e727–734.
- [15] Lindroth M, Mortenson V. Long-term follow-up of ventilator treated low birth-weight infants. I. Chest X-ray, pulmonary mechanics, clinical lung disease and growth. *Acta Paediatr Scand* 1986;75(5):819–26.
- [16] Greenough A, Giffin FJ, Yuksel B, Dimitriou G. Respiratory morbidity in young school children born prematurely—chronic lung disease is not a risk factor? *Eur J Pediatr* 1996;155(9):823–6.
- [17] Been JV, Lugtenberg MJ, Smets E, et al. Preterm birth and childhood wheezing disorders: a systematic review and meta-analysis. *PLoS Med* 2014;11(1):e1001596.
- [18] Fawke J, Lum S, Kirkby J, et al. Lung function and respiratory symptoms at 11 years in children born extremely preterm: the EPICure study. *Am J Respir Crit Care Med* 2010;182(2):237–45.
- [19] Vrijlandt EJ, Gerritsen J, Boezen HM, Duiverman EJ, Dutch P-CSG. Gender differences in respiratory symptoms in 19-year-old adults born preterm. *Respir Res* 2005;6:117.
- [20] Northway Jr. WH, Moss RB, Carlisle KB, et al. Late pulmonary sequelae of bronchopulmonary dysplasia. *N Engl J Med* 1990;323(26):1793–9.
- [21] May C, Kennedy C, Milner AD, Rafferty GF, Peacock JL, Greenough A. Lung function abnormalities in infants developing bronchopulmonary dysplasia. *Arch Dis Child* 2011;96(11):1014–9.
- [22] Gibson AM, Doyle LW. Respiratory outcomes for the tiniest or most immature infants. *Semin Fetal Neonatal Med* 2014;19(2):105–11.
- [23] Fakhoury KF, Sellers C, Smith EO, Rama JA, Fan LL. Serial measurements of lung function in a cohort of young children with bronchopulmonary dysplasia. *Pediatrics* 2010;125(6):e1441–1447.
- [24] Hennessy EM, Bracewell MA, Wood N, et al. Respiratory health in pre-school and school age children following extremely preterm birth. *Arch Dis Child* 2008;93(12):1037–43.
- [25] Brostrom EB, Thunqvist P, Adenfelt G, Borling E, Katz-Salamon M. Obstructive lung disease in children with mild to severe BPD. *Respir Med* 2010;104(3):362–70.
- [26] Doyle LW, Faber B, Callanan C, Freezer N, Ford GW, Davis NM. Bronchopulmonary dysplasia in very low birth weight subjects and lung function in late adolescence. *Pediatrics* 2006;118(1):108–13.
- [27] Cristea AI, Ackerman VL, Swigonski NL, Yu Z, Slaven JE, Davis SD. Physiologic findings in children previously ventilator dependent at home due to bronchopulmonary dysplasia. *Pediatr Pulmonol* 2015;50(11):1113–8.
- [28] Stern DA, Morgan WJ, Wright AL, Guerra S, Martinez FD. Poor airway function in early infancy and lung function by age 22 years: a non-selective longitudinal cohort study. *Lancet* 2007;370(9589):758–64.
- [29] Narang I, Rosenthal M, Cremonesi D, Silverman M, Bush A. Longitudinal evaluation of airway function 21 years after preterm birth. *Am J Respir Crit Care Med* 2008;178(1):74–80.
- [30] Vrijlandt EJ, Gerritsen J, Boezen HM, Grevink RG, Duiverman EJ. Lung function and exercise capacity in young adults born prematurely. *Am J Respir Crit Care Med* 2006;173(8):890–6.
- [31] MacLean JE, DeHaan K, Fuhr D, et al. Altered breathing mechanics and ventilatory response during exercise in children born extremely preterm. *Thorax* 2016;71(11):1012–9.
- [32] Welsh L, Kirkby J, Lum S, et al. The EPICure study: maximal exercise and physical activity in school children born extremely preterm. *Thorax* 2010;65(2):165–72.
- [33] Koroglu OA, Yalaz M, Levent E, Akisu M, Kultursay N. Cardiovascular consequences of bronchopulmonary dysplasia in prematurely born preschool children. *Neonatology* 2013;104(4):283–9.
- [34] Abman SH. The dysmorphic pulmonary circulation in bronchopulmonary dysplasia: a growing story. *Am J Respir Crit Care Med* 2008;178(2):114–5.
- [35] Telford K, Waters L, Vyas H, Manktelow BN, Draper ES, Marlow N. Respiratory outcome in late childhood after neonatal continuous negative pressure ventilation. *Arch Dis Child Fetal Neonatal Ed* 2007;92(1):F19–24.
- [36] Mandy G, Malkar M, Welty SE, et al. Tracheostomy placement in infants with bronchopulmonary dysplasia: safety and outcomes. *Pediatr Pulmonol* 2013;48(3):245–9.
- [37] Com G, Kuo DZ, Bauer ML, et al. Outcomes of children treated with tracheostomy and positive-pressure ventilation at home. *Clin Pediatr* 2013;52(1):54–61.
- [38] Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. *Lancet Neurol* 2009;8(1):110–24.
- [39] Keunen K, van Elburg RM, van Bel F, Benders MJ. Impact of nutrition on brain development and its neuroprotective implications following preterm birth. *Pediatr Res* 2015;77(1–2):148–55.
- [40] de Kieviet JF, Zoetebier L, van Elburg RM, Vermeulen RJ, Oosterlaan J. Brain development of very preterm and very low-birthweight children in childhood and adolescence: a meta-analysis. *Dev Med Child Neurol* 2012;54(4):313–23.
- [41] Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJ. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. *J Am Med Assoc* 2002;288(6):728–37.
- [42] Kerr-Wilson CO, Mackay DF, Smith GC, Pell JP. Meta-analysis of the association between preterm delivery and intelligence. *J Public Health* 2012;34(2):209–16.
- [43] Twilhaar ES, Wade RM, de Kieviet JF, van Goudoever JB, van Elburg RM, Oosterlaan J. Cognitive outcomes of children born extremely or very preterm since the 1990s and associated risk factors: a meta-analysis and meta-regression. *JAMA Pediatr* 2018;172(4):361–7.
- [44] Thompson DK, Warfield SK, Carlin JB, et al. Perinatal risk factors altering regional brain structure in the preterm infant. *Brain* 2007;130(Pt 3):667–77.
- [45] Short EJ, Klein NK, Lewis BA, et al. Cognitive and academic consequences of bronchopulmonary dysplasia and very low birth weight: 8-year-old outcomes. *Pediatrics* 2003;112(5):e359.
- [46] Perrone S, Tataranno LM, Stazzoni G, Ramenghi L, Buonocore G. Brain susceptibility to oxidative stress in the perinatal period. *J Matern Fetal Neonatal Med* 2015;28(Suppl 1):2291–5.
- [47] Perrone S, Tataranno ML, Buonocore G. Oxidative stress and bronchopulmonary dysplasia. *J Clin Neonatol* 2012;1(3):109–14.
- [48] Wilson-Costello D, Friedman H, Minich N, et al. Improved neurodevelopmental outcomes for extremely low birth weight infants in 2000–2002. *Pediatrics* 2007;119(1):37–45.
- [49] Baud O, Trousson C, Biran V, et al. Association between early low-dose hydrocortisone therapy in extremely preterm neonates and neurodevelopmental outcomes at 2 years of age. *J Am Med Assoc* 2017;317(13):1329–37.
- [50] Singer LT, Kercsmar C, Legris G, Orlowski JP, Hill BP, Doershuk C. Developmental sequelae of long-term infant tracheostomy. *Dev Med Child Neurol* 1989;31(2):224–30.
- [51] Rane S, Shankaran S, Natarajan G. Parental perception of functional status following tracheostomy in infancy: a single center study. *J Pediatr* 2013;163(3):860–6.
- [52] DeMauro SB, D'Agostino JA, Bann C, et al. Developmental outcomes of very preterm infants with tracheostomies. *J Pediatr* 2014;164(6):1303–10. e1302.
- [53] Luo J, Shepard S, Nilan K, et al. Improved growth and developmental activity post tracheostomy in preterm infants with severe BPD. *Pediatr Pulmonol* 2018;53(9):1237–44.



Hemodynamic management in chronically ventilated infants

Shazia Bhombal^a, Shahab Noori^{b,*}

^a Division of Neonatal and Developmental Medicine, Department of Pediatrics, Stanford University, Palo Alto, CA, USA

^b Fetal and Neonatal Institute, Division of Neonatology, Children's Hospital Los Angeles, Department of Pediatrics, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

ARTICLE INFO

Keywords:

Bronchopulmonary dysplasia
Diastolic dysfunction
Preterm infants
Pulmonary hypertension

ABSTRACT

Positive pressure ventilation can significantly alter hemodynamics. The reduction in systemic venous return and increase in right ventricular afterload in response to an inappropriately high mean airway pressure can decrease pulmonary blood flow and compromise systemic perfusion as a result. In addition to ventilator parameters, the degree of hemodynamic effects depends on the baseline cardiac function and lung compliance. Furthermore, the chronically ventilated infants often have a multitude of comorbidities which may also impact hemodynamics. These include pulmonary and systemic hypertension which can lead to myocardial dysfunction as a result of the increase in the right and left ventricular afterload, respectively. In this section, we aim to outline the hemodynamic changes associated with chronic lung disease and mechanical ventilation and discuss management options.

1. Introduction

An understanding of the heart lung interaction is crucial to grasping the impact chronic ventilation will have on the heart and circulation. The heart lung interaction is on a continuum, whether a patient is on mechanical support or breathing on their own. For a patient on assisted ventilation, lung overdistension can lead to hemodynamic alterations, with increased right ventricular (RV) afterload and decreased RV output, as well as decreased left ventricular (LV) filling and resultant decreased LV output [1]. While proximal airway pressure is routinely measured at the bedside, intrathoracic pressure is more difficult to estimate and therefore is not routinely monitored even though it has more hemodynamic relevance. The effect of respiratory cycle on the hemodynamics depends on whether the patient is spontaneously breathing or on mechanical ventilation (Fig. 1). For example, inspiration promotes systemic venous return in spontaneously breathing infant but could impede venous return in mechanically ventilated patients. On the other hand, mechanically ventilated patients have a more favorable intrathoracic interaction with the LV that allows for a lower transmural gradient and lower afterload thereby improving systemic perfusion [2].

In ventilated infants, it is important to closely monitor the lung expansion, as inappropriately high mean airway pressure (MAP) leads to lung overdistention and compression of alveolar vessels resulting in decreased pulmonary blood flow and decreased cardiac output (Fig. 2). Similarly, low lung volume can increase pulmonary vascular resistance

by increasing tortuosity of extra-alveolar vessels [3]. To a lesser degree, even during the respiratory cycle pulmonary vascular resistance changes with the lowest pulmonary vascular resistance occurring at functional residual capacity, during end expiration [4]. In addition to the effect on pulmonary vascular resistance, inappropriately high mean airway pressure can also lead to decreased systemic venous return. In such a case, volume administration targeting a higher central venous pressure (CVP) may help with RV filling, though this is not well elucidated in the neonatal literature [5]. There is a fine balance in chronically ventilated patients to attain the optimal positive end-expiratory pressure (PEEP) to allow for aeration of heterogeneous lung parenchyma to ensure the best ventilation/perfusion (V/Q) matching, without overdistending the lung. In a study evaluating changes in PEEP on hemodynamics in the preterm neonate after acute phase of respiratory distress syndrome, an increase in PEEP from 0 to 8 cmH₂O resulted in an approximately 25–30% decrease in biventricular stroke volume, with significant difference from 4 to 8 cmH₂O, without significant change in heart rate, thus resulting in decreased cardiac output [6]. On the other hand, in premature patients with a patent ductus arteriosus (PDA), an increase in PEEP from 5 to 8 cmH₂O did not alter systemic perfusion except for a mild reduction in LV output presumably due to reduction in PDA shunt [7]. Indeed, other investigators have also found milder effect PEEP or MAP on hemodynamic when the lungs have low compliance [8]. With a poorly compliant lungs, the airway pressure is not as readily transmitted to the pulmonary

* Corresponding author. Division of Neonatology, Children's Hospital Los Angeles, 4650 Sunset Blvd, MS#31 Los Angeles, CA 90027, USA.
E-mail address: snoori@chla.usc.edu (S. Noori).

<https://doi.org/10.1016/j.siny.2019.101038>

Abbreviations

ACE	angiotensin converting enzyme
BPD	bronchopulmonary dysplasia
CT	computerized tomography
CVP	central venous pressure
ELBW	extremely low birth weight
IUGR	intrauterine growth restriction

iNO	inhaled nitric oxide
LV	left ventricle
MAP	mean airway pressure
MRI	magnetic resonance imaging
PDA	patent ductus arteriosus
PEEP	positive end-expiratory pressure
RV	right ventricle
V/Q	ventilation/perfusion

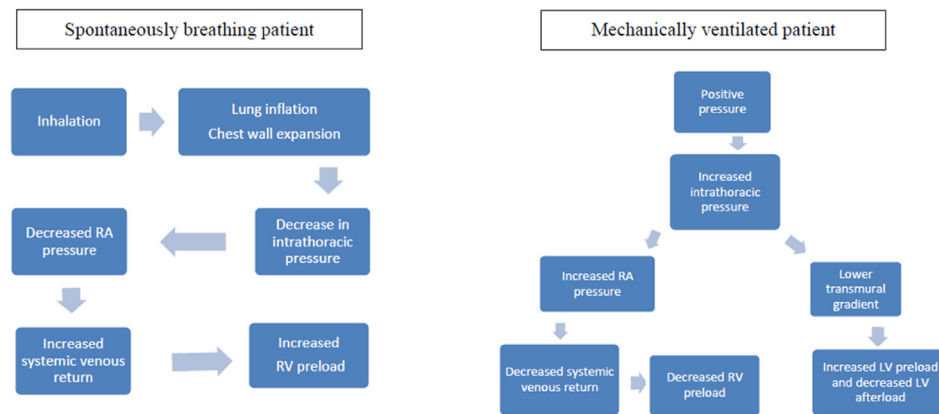


Fig. 1. The effect of spontaneous respiration versus mechanical ventilation on the hemodynamics.

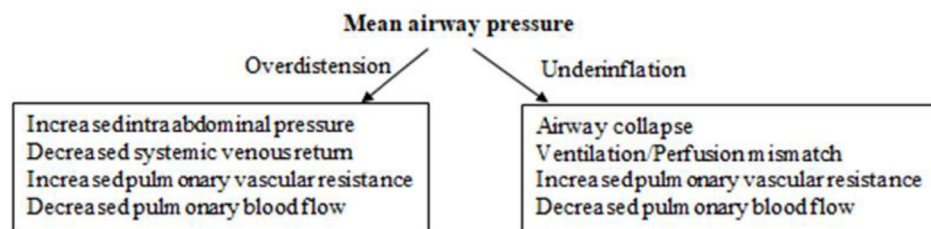


Fig. 2. Effect of mean airway pressure on hemodynamics.

vasculature as compared to a compliant lung. For example, an infant with chronic lung disease, may have little variability in hemodynamics with a change in PEEP from 6 to 8 cmH₂O, whereas a ventilated patient with an upper airway anomaly who has compliant lungs will have a more hemodynamic alteration with such a change. This must be kept in mind when considering increasing PEEP to affect pulmonary or systemic blood flow. The literature is contradictory regarding the effect of noninvasive mechanical ventilation on hemodynamics, perhaps due to differential transmission of pressure via noninvasive route. One study evaluating continuous positive airway pressure of 5 cmH₂O in preterm infants reported a decrease in RV output and reduction in the size of right and left sided structures, with no effect on PDA shunt [9]. However, a similar study did not find any effect on cardiac output and size [10].

In chronically ventilated infants with pulmonary hypertension, increased pulmonary vascular resistance due to lung overdistension may even be more problematic and could exacerbate the RV dysfunction prevalent in this population (see below). In addition, systemic circulation could be compromised due to ventricular interdependence. Indeed, distortion of the RV and septal flattening impacts LV function and filling through ventricular-ventricular interaction [4,11].

Chronically ventilated infants are comprised of broad differential diagnoses, including lung hypoplasia, neuromuscular disease, central hypoventilation disorders, airway anomalies, and bronchopulmonary dysplasia (BPD). Former preterm neonates comprise a majority of infants requiring mechanical support, and this patient population is

particularly at risk for further comorbidities that will affect their hemodynamic management.

2. Pulmonary hypertension in chronic lung disease

Chronic lung disease of the premature neonate comprises a large number of chronically ventilated infants and is the most common complication of preterm birth. BPD was first described in 1967 by Northway and colleagues and comprised of patients with gestational ages ranging from 30 to 39 weeks with resultant inflammation, fibrosis and scarring of the pulmonary vascular bed due to factors including mechanical support and oxygen toxicity [12,13]. As the threshold of viability has moved to 22–24 weeks' gestation, a newer form of BPD has emerged. This “new BPD” is characterized by arrest in lung development [14]. Over the last decade, the development of pulmonary hypertension has increasingly been recognized in this population.

2.1. Pathogenesis

Lung development spans five stages, embryonic (4–7 weeks), pseudoglandular (7–17 weeks), canalicular (17–24 weeks), saccular (24–36 weeks), and alveolar stages (36 weeks–2 years). Preterm birth results in arrest of lung development at the late canalicular or early saccular stages, resulting in abnormal pulmonary vascular development and remodeling. This arrest of development leads to impairment of the dual mechanisms of vascular growth, angiogenesis (extension of

existing vascular network with eventual formation of alveolar capillary network) and vasculogenesis (development and differentiation of mesenchymal cells into vascular networks) [15–17]. The pathogenesis of pulmonary vascular disease in preterm neonates is multifactorial, including prenatal and postnatal factors, hypoxia, hyperoxia, inflammation, and baro- and volutrauma associated with mechanical ventilation (Fig. 3). Many of these factors influence proangiogenic genes such as vascular endothelial growth factor (VEGF) [18]. VEGF is essential in vascular network development, with animal studies demonstrating that alterations in expression with mechanical ventilation and hyperoxia decrease VEGF expression [19,20]. Numerous other signaling pathways such as soluble fms-like tyrosine kinase-1 (sFlt-1) and hypoxia-inducible factor 1 (HIF-1) also play an important role in vascular development. Contributions of these factors in development of pulmonary vascular disease in BPD requires further studies [18,21].

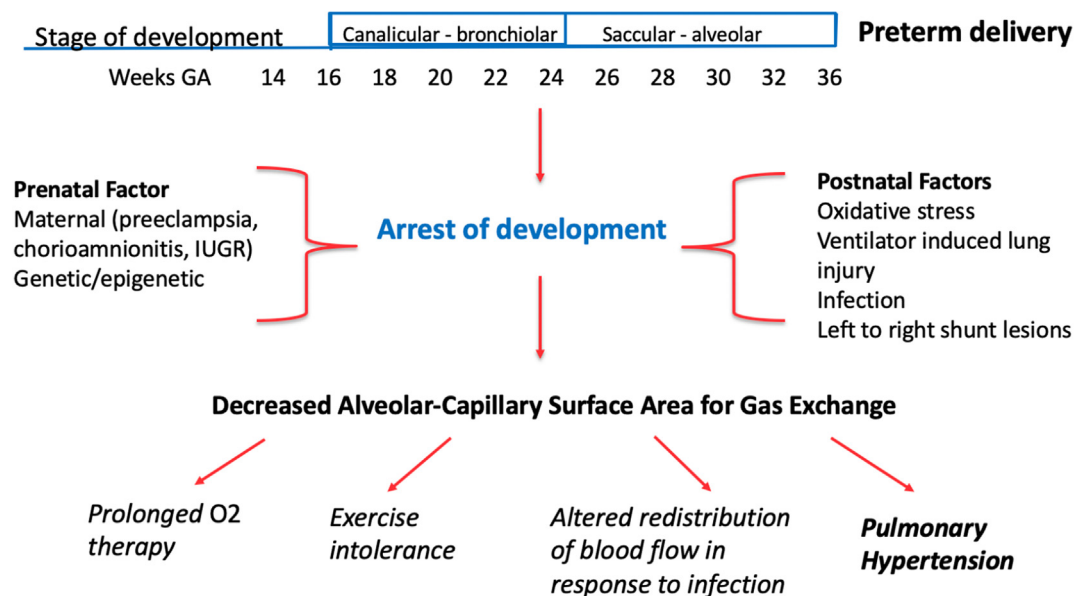
In addition to alterations in vascular development, increased muscularization of the peripheral pulmonary vasculature is noted in the preterm neonate. Decreased vascular network and increased muscularization of the peripheral pulmonary vasculature places preterm neonates at risk for development of pulmonary hypertension [22]. Premature neonates with severe BPD have a higher incidence of pulmonary hypertension than those with mild or no BPD [23,24]. Thus, chronically ventilated preterm infants are at high risk of developing pulmonary hypertension. The propensity for development of pulmonary hypertension may be identified early in the postnatal course. Diagnosis of pulmonary hypertension ranges from 6 to 43% between 1 and 6 weeks after birth with this finding being predictive of both pulmonary hypertension at 36 weeks postnatal age and increased severity of BPD [23,24]. The observation that premature neonates with signs of pulmonary hypertension on echocardiography at 7 days of life have a higher incidence of pulmonary hypertension later on, suggests that early pulmonary vascular disease may play a role in development of pulmonary hypertension in the preterm population [23]. Another potential contributor for development of pulmonary hypertension in BPD is decreased placental perfusion leading to chronic hypoxia [25].

2.2. Diagnosis and screening

Identification of patients with pulmonary hypertension is crucial, as diagnosis of pulmonary hypertension in a preterm neonate is associated with an increased risk of morbidity and mortality, with one study reporting a survival rate of 64% at 6 months and 52% two years after diagnosis of pulmonary hypertension [26]. Until recently, diagnosis of pulmonary hypertension often occurred after the first few postnatal months [26]. However, with increased awareness, pulmonary hypertension is more likely to be recognized during the initial hospitalization. In one study, over a 5-year period, all the extremely low birth weight (ELBW) infants received an echocardiogram when BPD was diagnosed or prior to discharge and at least one more echocardiogram after discharge [27]. Eighteen percent of the ELBW infants had pulmonary hypertension with 41% identified after discharge [27] hence the recommendation of close follow up as outpatient [26,28]. In a recent study, adults with a history of prematurity at < 29 weeks' gestation but no notable cardiorespiratory compromise underwent catheterization and found to have increased resting pulmonary artery pressures and elevated pulmonary vascular resistance compared with adults born at term [29]. Eighteen percent of adults born preterm were diagnosed with pulmonary hypertension and an additional 27% had borderline elevated pulmonary artery pressures. The authors found that number of days with assisted ventilation (non-invasive and invasive) correlated more with incidence of elevated pulmonary artery pressures as an adult than gestational age. While further studies are needed to fully assess the impact pulmonary vascular disease has on an individual born preterm, screening for pulmonary hypertension in the chronically ventilated preterm neonate appears prudent.

With a relatively high prevalence of pulmonary hypertension in the chronically ventilated preterm infant, the American Heart Association and American Thoracic Society in 2015 released guidelines recommending screening for pulmonary hypertension in the patient with BPD [30]. A recent expert consensus statement from the Pediatric Pulmonary Hypertension Network recommended screening

Pathophysiology of PH in BPD



Adapted from Mourani, Curr Opin Pediatr 2013

Fig. 3. Pathophysiology of BPD associated pulmonary hypertension [69,70].

echocardiograms in the patient with BPD, particularly in patient with persistent high oxygen requirements and prolonged mechanical ventilation at 36 weeks postmenstrual age [28]. In a recent survey of neonatologists, while a majority performed screening echocardiograms on their preterm neonates with BPD at 36 weeks gestational age, only 38% had an institutional screening protocol [31]. Patient characteristics that increase the risk of development of pulmonary hypertension and therefore warrant screening include hypercarbia, poor growth, and feeding difficulties [32].

2.2.1. Cardiac catheterization

Cardiac catheterization is considered the gold standard for assessment of pulmonary hypertension, with the 2015 AHA guidelines recommending cardiac catheterization for patients with BPD prior to initiation of medications. However, this procedure is not without risk, particularly in the population with chronic lung disease. In a retrospective study of children undergoing catheterization for pulmonary vasoreactivity testing, 6% resulted in resuscitation or death [33]. Institutional experience in the management of patients with pulmonary hypertension particularly important in chronically ventilated infants when performing catheterizations in this population as children under 2 years of age have an increased risk of complications from cardiac catheterization compared to the older pediatric population [34]. While catheterization at the time of initial diagnosis of pulmonary hypertension in the chronically ventilated infants may not be indicated, catheterization may be appropriate in cases such as need for multiple pulmonary vasodilators, evaluation of shunt lesions (atria and ventricular septal defect, PDA) or concern for impaired LV function and pulmonary vein stenosis. Goals of catheterization include assessment of severity of pulmonary hypertension, obtain pulmonary venous saturations for pulmonary contribution, assessment for pulmonary vein stenosis, and perform acute pulmonary reactivity testing [28].

2.2.2. Echocardiography

While cardiac catheterization is the gold standard for diagnosis of pulmonary hypertension, echocardiography is the most utilized and effective noninvasive method for assessment. Although inter- and intra-rater agreement is fairly high in diagnosing pulmonary hypertension in the preterm infant [35,36], utilization of echocardiography for identification of pulmonary hypertension must be done with caution. In comparison to catheterization, only presence of tricuspid regurgitation jet and resultant estimated elevation in pulmonary artery pressure had good correlation with elevated pulmonary vascular resistance by catheterization. However, a reliable tricuspid regurgitation jet velocity is obtained only in approximately 61% of pediatric echocardiographic

studies [37].

Evaluation by echocardiography involves assessment of multiple parameters as a reflection of increased RV afterload in the presence of elevated pulmonary vascular resistance. Echocardiographic assessment of pulmonary hypertension in the patient with BPD includes assurance of normal intracardiac anatomy, assessment of right and left ventricular size and function, interventricular septal positioning, estimation of pulmonary artery pressure through evaluation of tricuspid and pulmonary regurgitation velocities as well as assessment of flow through shunts (ventricular septal defect, PDA) (Table 1 and Fig. 4) [28]. Recording systolic blood pressure at the time of the echocardiogram is utilized for comparison with pulmonary artery pressure estimation. Many of the standard measurements involve an imprecise qualitative judgement, and more advanced echocardiographic measures of pulmonary hypertension are being introduced in this population allowing for more quantifiable assessment (Table 1).

2.2.3. Other modalities

Other modalities of screening for pulmonary hypertension in the infant with BPD include electrocardiogram (EKG), with diagnosis of pulmonary hypertension consistent with right atrial enlargement, right axis deviation, and right ventricular hypertrophy, though right axis deviation is normal in the neonate, with right ventricle to left ventricle ratio normalizing by 6 months of age [38,39]. Serial EKGs may be useful in following for development of right sided changes [40]. High resolution contrast enhanced computerized tomography (CT) scan is quick, does not require anesthesia, and provides information on severity of the lung parenchyma disease, presence of pulmonary vein stenosis, thromboembolic disease and airway diseases [41,42]. While magnetic resonance imaging (MRI) is not routinely utilized in the assessment of pulmonary hypertension in the pediatric population, it has a role in assessment of RV size and function in the congenital heart disease realm. In a review of pediatric cardiac MRIs performed for pulmonary hypertension, RV ejection fraction and LV stroke volume index correlated most strongly with survival [43]. The ability to perform an MRI without sedation and radiation make it an attractive option, and further studies needed to demonstrate standardization of use in the pediatric pulmonary hypertension population.

2.3. Management

Treatment of pulmonary hypertension in the chronically ventilated infant encompasses optimizing ventilatory management and addressing inflammation and pulmonary edema prior to initiation of pulmonary vasodilator therapy. A thorough evaluation of the airway is warranted

Table 1
Echocardiographic parameters in patients with BPD associated pulmonary hypertension.

	Parameter	Markers of PH
Conventional Echocardiographic Measures	Right ventricular size	Dilation, hypertrophy
	Tricuspid regurgitation Doppler peak (Estimates RV systolic pressure)	> 3–3.5 m/s consistent with PH, compare pressure with systolic blood pressure
	Pulmonary insufficiency Doppler peak (Estimates mean pulmonary artery pressure)	> 25 mmHg
	Shunt assessment	Direction and velocity of flow across VSD, PDA provides pressure estimates
Advanced Echocardiographic Measures	Septal geometry	Flattening or bowing into LV consistent with PH
	LV Eccentricity index (Ratio of LV measured perpendicular compared to parallel in parasternal short axis)	Increased
	Tricuspid Annular Plane Systolic Excursion (TAPSE) (Movement of tricuspid valve along lateral RV wall as assessment of RV function)	Decreased
	RV Fractional area of change (RV FAC – measurement of RV function)	Decreased
	Pulmonary artery acceleration time (PAAT) and PAAT/ET (ejection time)	Decreased

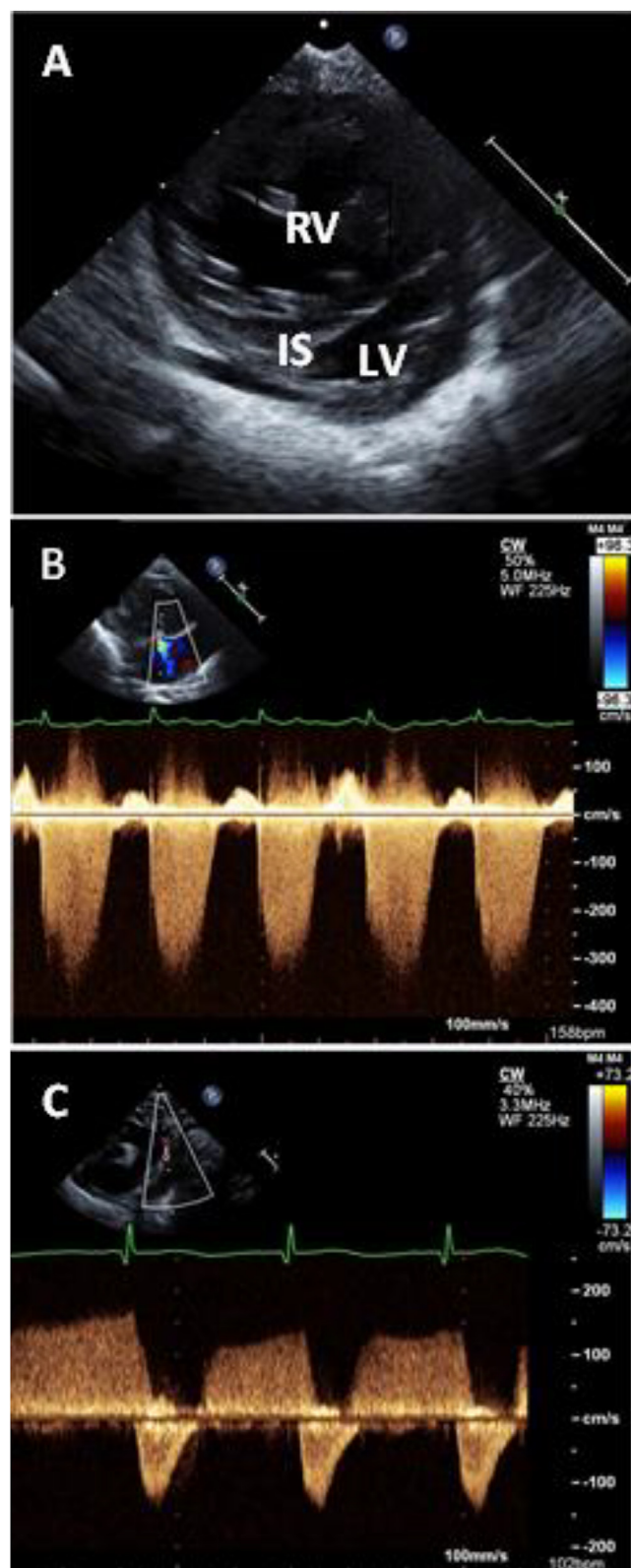


Fig. 4. Echocardiographic images of pulmonary hypertension. A. Parasternal short axis view demonstrating dilated right ventricle (RV) and flattened interventricular septum into the left ventricle, consistent with severe pulmonary hypertension. B. Tricuspid regurgitation Doppler demonstrating peak regurgitant velocity. C. Bidirectional flow across the PDA with flow below the baseline demonstrating right to left flow during systole, consistent with elevated pulmonary pressures. RA = right atrium, RV = right ventricle, IS = interventricular septum, LV = left ventricle.

including assessment for malacia and vocal cord paralysis (particularly in patients who have undergone PDA ligation, with incidence of vocal cord paralysis ranging from 11 to 67%) [44,45]. Oxygen saturation target in this population is 92–95%, with even brief, intermittent periods of hyperoxia associated with elevated pulmonary artery pressures by catheterization [28,46]. While there is no silver bullet for management of BPD associated pulmonary hypertension, numerous pulmonary vasodilators have been utilized (Table 2) [28,47]. Sildenafil is the most studied in this population, though data is limited. It is the most readily administered agent and is generally well tolerated orally. Of note, sildenafil has the potential to worsen V/Q mismatch in patients with significant lung disease and heterogeneity, as well as increase gastroesophageal reflux symptoms and close monitoring is warranted to assess effect on the individual patient. Further studies are needed to determine the choice and duration of the best medications for management of pulmonary hypertension in this population.

2.4. Outcome

In a multicenter retrospective cohort study of 1677 patients < 32 weeks' gestational age, increased morbidity and mortality were noted among infants with BPD and pulmonary hypertension (22%). In addition, 38% of infants with BPD and pulmonary hypertension were readmitted over the first year of life. Furthermore, they were more likely to be discharged home with tube feeds, a tracheostomy, and supplemental oxygen [48]. Therefore, a multidisciplinary team approach is warranted in this complex population. Indeed, coordination of care is needed to facilitate transition from inpatient to outpatient care with optimization of cardiorespiratory management and nutritional support, and to ensure neurodevelopmental follow-up [28,49].

3. Pulmonary vein stenosis

When imaging the chronically ventilated infant with BPD and pulmonary hypertension, pulmonary veins should also be evaluated. Pulmonary vein stenosis (PVS) is estimated to occur in approximately 2 cases per 100,000 annually, with most cases associated with preterm birth [50]. Infants with BPD and PVS have a mortality risk of 45–50% within the first two years of diagnosis [51,52]. PVS in the preterm neonate appears to be an acquired disease, diagnosed at an average of 6.5 months with approximately 3–5 echocardiograms obtained prior to finding PVS. Thus, continued evaluation of the pulmonary veins on serial echocardiograms is important for diagnosis. If echocardiogram is difficult to obtain (for example, poor acoustic windows), and there is a concern about presence of PVS, CT angiography should be considered. A recent study found the risk of increased mortality to be associated with stenosis of more than 2 pulmonary veins, bilateral PVS, small for gestational age, and < 6 months of age at diagnosis [52]. There is recent intriguing research on utilizing chemotherapy agents to impact multivessel pulmonary vein disease resulting in increased survival of 77% at 72 weeks [53]. Further studies are needed to understand the etiology and potential targets for prevention and therapy, as catheterization or surgical intervention is unsatisfactory, with restenosis often occurring in up to 44% [52].

4. Systemic hypertension

Patients with chronic lung disease are at increased risk for developing systemic hypertension which affects LV afterload and could alter hemodynamics. The incidence of systemic hypertension in the neonatal period has been reported from 0.2 to 3%, however patients with BPD have been noted to have an increased incidence of systemic hypertension [54]. The association of systemic hypertension with BPD was initially reported in 1984 with 43% of preterm neonates developing systemic hypertension in their first year of life, with a mean onset of 4.8 months [55]. While a later study demonstrated a lower incidence of

Table 2
Pharmacotherapy for pulmonary hypertension in the chronically ventilated infant.

Pathway	Medication	Mechanism of action (MOA)
cGMP	Inhaled nitric oxide	Lead to production of cGMP, relaxation of vascular smooth muscle, vasodilation
	Sildenafil	Phosphodiesterase 5 inhibitor, prevents breakdown of cGMP, potentiating vasodilation by relaxation of vascular smooth muscle
cAMP	Iloprost (inhaled, IV)	Activates adenylate cyclase leading to increased cAMP and vascular smooth muscle relaxation, half-life 20–30 min by inhalation
	Treprostinil (inhaled, IV, SC)	Remodulin, same MOA as Iloprost, half-life 3 h
	Eprostenol IV	Flolan, Same MOA as Iloprost, short half-life of 6 min, continuous infusion
	Milrinone IV	Phosphodiesterase 3 inhibitor, prevents breakdown of cAMP, potentiating vasodilation by relaxation of vascular smooth muscle
Endothelin	Bosentan	Endothelin 1 antagonist, affecting both endothelin A (ET _A , vasoconstriction) and B (ET _B , vasodilation) receptors

13% diagnosed in the first year, it is reasonable to conclude that patients with BPD should be monitored for development of systemic hypertension. Patients with severe BPD (as defined in early studies by home oxygen requirement) comprised the majority of premature patients with systemic hypertension, with early studies defining hypertension as systolic blood pressure greater than 115 mmHg [55,56]. A recent multicenter study reviewed incidence of systemic hypertension in 18 institutions over nearly 20 years and found a similar incidence of unexplained systemic hypertension in preterm patients with and without chronic lung disease. Patients developed systemic hypertension between 3.5 and 4 months of age and generally resolved over the subsequent two years [57].

Numerous potential causes have been suggested for development of systemic hypertension in the preterm neonate. Umbilical artery catheter thrombosis is recognized as the most common renovascular cause of systemic hypertension in neonates, potentially resulting from endothelial damage at the time of catheter placement [54]. Another intriguing prospect is the effect lung disease has on circulating levels of norepinephrine. In the lamb model, norepinephrine was found to have decreased clearance during periods of hypoxia [58]. It is plausible that increased levels of circulating norepinephrine could contribute to elevated systolic blood pressure in the preterm neonate. In the adult population with chronic lung disease, increased arterial stiffness has been noted [59]. Interestingly, a recent study in the BPD population also demonstrated increased aortic wall thickness and stiffness [60]. The authors surmised that increased systemic vascular thickness could be a factor in elevated systolic blood pressure. Recognition of systemic hypertension in patients with BPD is important as it may affect LV structure and systolic and diastolic function [61].

Given the impact on the LV function and the risk for cardiac hypertrophy and heart failure early recognition and treatment of hypertension is recommended [62,63].

Vasodilators such as hydralazine are among the most commonly used antihypertensive agents, followed by angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, and alpha- and beta-blockers [64]. In neonates, ACE inhibitors can evoke an exaggerated response leading to hypotension and therefore should be started with a low dose. Furthermore, due to possible adverse effect on renal development, some have recommended it only after 44 weeks postmenstrual age [63]. While there is a dearth of literature on the management of systemic hypertension in the setting of chronic lung disease, use of diuretics such as spironolactone, at times paired with a thiazide agent, may be a useful first line treatment. In chronically ventilated neonates, beta blockers should be used with caution as it can exacerbate the chronic lung disease.

5. Diastolic dysfunction in chronic lung disease

Diastolic dysfunction is a well-known entity in the adult literature. However, in infants this diagnosis is not well defined, though is becoming more recognized in neonates, especially in preterm infants with chronic lung disease. Diastolic dysfunction includes decreased myocardial compliance and impairment in relaxation of the myocardium and can result from numerous etiologies. Premature myocardium is inherently poorly compliant. As for impairment in myocardial relaxation, other than cases of cardiomyopathy such as hypertrophic cardiomyopathy of infants of diabetic mothers [65], the underlying cause is unclear. In the adult population, diastolic dysfunction is considered in many disease states, including in patients with pulmonary hypertension or increased pulmonary edema.

In fetal life, the RV is the dominant ventricle and provides about 60% of the combined cardiac output. As a result, and the RV is thickened at birth, with improvement in relaxation occurring over time. Shortly after birth, LV afterload increases with removal of the low resistance placental circulation, and the LV is suddenly faced with an increased workload. In addition, the LV is exposed to a large change in volume with increased pulmonary venous return. The left ventricle adapts to postnatal life, with the LV diastolic function improving in the neonate over time. Echocardiography allows for assessment of the left ventricular diastolic flow parameters and changes over time. Normal LV filling occurs primarily through passive filling (E wave on Doppler of mitral valve inflow). The late atrial contraction (A wave on Doppler of mitral inflow) provides a smaller portion of the LV filling. However, with decreased LV compliance particularly in the first month of life in the preterm neonate, there is E/A wave reversal, with more flow entering the LV from the atrial contraction (Fig. 5). Preterm and term waveforms differ initially, with differences disappearing by the first month of life [66]. LV diastolic dysfunction has been associated with steroid use, particularly with dexamethasone, leading to LV hypertrophy in the preterm population, though this appears to normalize over time [67]. As discussed earlier, the higher prevalence of systemic hypertension in patients with chronic lung disease may result in diastolic dysfunction. Indeed, diastolic dysfunction has been reported in patients with severe BPD. This is important as treatment of BPD-associated pulmonary hypertension with pulmonary vasodilators could potentially worsen respiratory status in the subset with diastolic dysfunction. Addressing diastolic dysfunction utilizing afterload reduction and diuretics may be helpful in this population [68].

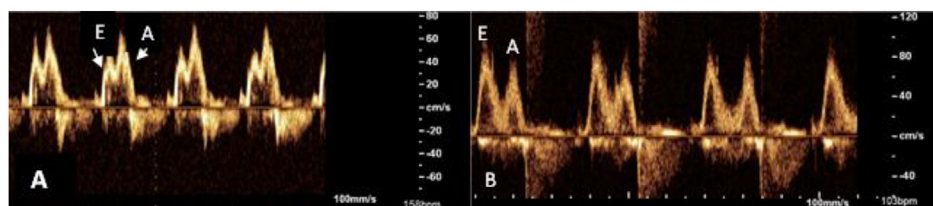


Fig. 5. Mitral valve inflow Doppler. A. Normal E/A ratio in a 7 day old preterm neonate with a larger atrial kick component of ventricular filling (A wave), compared with initial passive filling (E wave) B. Normal E/A ratio in a 10 month old infant, with majority of left ventricular filling occurring passively during initial opening of the valve (E wave).

6. Conclusions

Chronic mechanical ventilation has direct effects on hemodynamics by altering the loading condition and pulmonary vascular resistance. However, multiple comorbidities in the infants that require mechanical ventilation, notably those with a history of prematurity, have the potential to affect cardiac function. Comprehensive evaluation and assessment of hemodynamics in the chronically ventilated infant, especially for pulmonary and systemic hypertension, is essential, as they affect cardiorespiratory function over time. In addition, assessment of diastolic function and treatment targeting diastolic dysfunction may be helpful in management of chronically ventilated infants.

Declaration of competing interest

No conflict of interest for either or the authors and no funding source.

Learning Points

1. Positive pressure ventilation impacts cardiac mechanics and must be considered when managing a chronically ventilated infant.
2. Patients with chronic lung disease have an increased risk of developing pulmonary hypertension.
3. Patients with chronic lung disease are at risk for developing systolic hypertension.
4. Diastolic dysfunction with elevated left sided pressures can impact ventilation management and pulmonary edema in the chronically ventilated patient and should be recognized and managed appropriately.

Research Directions

1. Identifying chronically ventilated infants at risk for development of pulmonary hypertension.
2. The long-term effects of pulmonary vasodilators in chronically ventilated infants with pulmonary hypertension.
3. The interaction between systemic hypertension and chronic lung disease; particularly in chronically ventilated infants with LV diastolic dysfunction.
4. The role of diastolic dysfunction in pathogenesis of chronic lung disease.

References

- [1] Noori S, Kluckow M. Pulmonary-Cardiovascular interaction. In: Bancalari E, Keszler M, Davis P, editors. Neonatology: questions and controversies series: the newborn lung. Saunders; 2018.
- [2] Cheifetz IM. Cardiorespiratory interactions: the relationship between mechanical ventilation and hemodynamics. *Respir Care* 2014;59(12):1937–45.
- [3] Shekerdemian L, Bohn D. Cardiovascular effects of mechanical ventilation. *Arch Dis Child* 1999;80(5):475–80.
- [4] Grubler MR, Wigger O, Berger D, Bloechlinger S. Basic concepts of heart-lung interactions during mechanical ventilation. *Swiss Med Wkly* 2017;147:w14491.
- [5] Qvist J, Pontoppidan H, Wilson RS, Lowenstein E, Laver MB. Hemodynamic responses to mechanical ventilation with PEEP: the effect of hypervolemia. *Anesthesiology* 1975;42(1):45–55.
- [6] Hausdorf G and Hellwege HH. Influence of positive end-expiratory pressure on cardiac performance in premature infants: a Doppler-echocardiographic study. *Crit Care Med*. 198; 15: 661–664.
- [7] Fajardo MF, Claire N, Swaminathan S, Sattar S, Vasquez A, D'Ugard C, Bancalari E. Effect of positive end-expiratory pressure on ductal shunting and systemic blood flow in preterm infants with patent ductus arteriosus. *Neonatology* 2014;105:9–13.
- [8] de Waal KA, Evans N, van der Lee J, van Kaam A. Effect of lung recruitment on pulmonary, systemic, and ductal blood flow in preterm infants. *J Pediatr* 2009;154:651–5.
- [9] Abdel-Hady H, Matter M, Hammad A, El-Refaay A, Aly H. Hemodynamic changes during weaning from nasal continuous positive airway pressure. *Pediatrics* 2008;122(5):1086–90.
- [10] Moritz B, Fritz M, Mann C, Simma B. Nasal continuous positive airway pressure (n-CPAP) does not change cardiac output in preterm infants. *Am J Perinatol* 2008;25(2):105–9.
- [11] Yamaguchi S, Harasawa H, Li KS, et al. Comparative significance in systolic ventricular interaction. *Cardiovasc Res* 1991;25:774–83.
- [12] Northway Jr. WH, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. *N Engl J Med* 1967;276:357–68.
- [13] Bancalari E, Claire N. Definitions and diagnostic criteria for bronchopulmonary dysplasia. *Semin Perinatol* 2006;30:164–70.
- [14] Jobe AH. The new bronchopulmonary dysplasia. *Curr Opin Pediatr* 2011;23(2):167–72.
- [15] Schittny JC. Development of the lung. *Cell Tissue Res* 2017;367(3):427–44.
- [16] Flamme I, Risau W. Induction of vasculogenesis and hematopoiesis in vitro. *Development* 1992;116:435–9.
- [17] Flamme I, Frolich T, Risau W. Molecular mechanisms of vasculogenesis and embryonic angiogenesis. *J Cell Physiol* 1997 Nov;173(2):206–10.
- [18] Alvira CM. Aberrant pulmonary vascular growth and remodeling in bronchopulmonary dysplasia. *Front Med* 2016;3:21.
- [19] Maniscalco WM, Watkins RH, D'Angio CT, Ryan RM. Hyperoxic injury decreases alveolar epithelial cell expression of vascular endothelial growth factor (VEGF) in neonatal rabbit lung. *Am J Respir Cell Mol Biol* 1997;16(5):557–67.
- [20] Maniscalco WM, Watkins RH, Pryhuber GS, Bhatt A, Shea C, Huyck H. Angiogenic factors and alveolar vasculature: development and alterations by injury in very premature baboons. *Am J Physiol Lung Cell Mol Physiol* 2002;282(4):L811–23.
- [21] Baker CD, Abman SH, Mourani PM. Pulmonary hypertension in preterm infants with bronchopulmonary dysplasia. *Pediatr Allergy Immunol Pulmonol* 2014 Mar 1;27(1):8–16.
- [22] Gorenflo M, Vogel M, Obladen M. Pulmonary vascular changes in bronchopulmonary dysplasia: a clinicopathologic correlation in short- and long-term survivors. *Pediatr Pathol* 1991;11(6):851–66.
- [23] Mourani PM, Sontag MK, Younoszai A, et al. Early pulmonary vascular disease in preterm infants at risk for bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2015 Jan 1;191(1):87–95.
- [24] Bhat, et al. Prospective analysis of pulmonary hypertension in extremely low birth weight infants. *Pediatrics* 2012;120:1260–9.
- [25] Mestan KK, Check J, Minturn L, et al. Placental pathologic changes of maternal vascular underperfusion in bronchopulmonary dysplasia and pulmonary hypertension. *Placenta* 2014;35:570–4.
- [26] Khemani E, McElhinney DB, Rhein L, Andrade O, et al. Pulmonary artery hypertension in formerly preterm infants with bronchopulmonary dysplasia: clinical features and outcomes in the surfactant era. *Pediatrics* 2007;120(6):1260–9.
- [27] Mehler K, et al. An echocardiographic screening program helps to identify pulmonary hypertension in extremely low birth weight infants with and without bronchopulmonary dysplasia: a single-center experience. *Neonatology* 2018;113:81–8.
- [28] Krishnan U, Feinstein JA, Adatia I, et al. Evaluation and management of pulmonary hypertension in children with bronchopulmonary dysplasia. *J Pediatr* 2017 Sep;188:24–34.
- [29] Goss KN, Behish AG, Barton GP, et al. Early pulmonary vascular disease in young adults born preterm. *Am J Respir Crit Care Med* 2018;198(12):1549–58.
- [30] Abman SH, et al. Pediatric pulmonary hypertension; guidelines from the American heart association and American thoracic society. *Circulation*; 2015.
- [31] Altit G, Lee HC, Hintz S, Tacy TA, Feinstein JA, Bhombal SB. Practices surrounding pulmonary hypertension and bronchopulmonary dysplasia amongst neonatologists caring for premature infants. *J Perinatol* 2018;38:361–7.
- [32] Abman SH, Grenolds A, Mourani P. Pulmonary vascular disease in bronchopulmonary dysplasia. *Adv Pulm Hypertens* 2016;15(2):91–9.
- [33] Taylor CJ, Derrick G, McEwan A, Haworth SG, Sury MRJ. Risk of cardiac catheterization under anaesthesia in children with pulmonary hypertension. *Br J Anaesth* 2007;98:657–61.
- [34] Zuckerman WA, Turner ME, Kertein J, Torres A, Vincent JA, Krishnan U, Kerstein D, Rosenzweig EB. Safety of cardiac catheterization at a center specializing in the care of patients with pulmonary arterial hypertension. *Pulm Circ* 2013;3(4):831–9.
- [35] Carlton EF, Sontag MK, Younoszai A, et al. Reliability of echocardiographic indicators of pulmonary vascular disease in preterm infants at risk for bronchopulmonary dysplasia. *J Pediatr* 2017;186:29–33.
- [36] McCrary AW, Barker PCA, Torok RD, et al. Agreement of an echocardiogram-based diagnosis of pulmonary hypertension in infants at risk for bronchopulmonary dysplasia among masked reviewers. *J Perinatol* 2019;39:248–55.
- [37] Mourani PM, Sontag MK, Younoszai A, Ivy DD, Abman SH. Clinical utility of echocardiography for the diagnosis and management of pulmonary vascular disease in young children with chronic lung disease. *Pediatrics* 2008;111:317–25.
- [38] Rosenzweig EB, Feinstin JA, Humpal T, Ivy DD. Pulmonary arterial hypertension in children: diagnostic work-up and challenges. *Prog Pediatr Cardiol* 2009 December;27(1):4–11.
- [39] Goodacre S, McLeod K. Paediatric electrocardiography. *BMJ* 2002;324:1382–5.
- [40] Abman SH. Monitoring cardiovascular function in infants with chronic lung disease of prematurity. *Arch Dis Child Fetal Neonatal Ed* 2002;87:F15–8.
- [41] Del Cerro MJ, Moledina S, Haworth SG, et al. Cardiac catheterization in children with pulmonary hypertensive vascular disease: consensus statement from the pulmonary vascular research institute, pediatric and congenital heart disease task forces. *Pulm Circ* 2016;6(1):118–25.
- [42] Latus H, Kuehne T, Beerbaum P, Apitz C, Hansmann G, Muthurangu V, Moledina S. Cardiac MR and CT imaging in children with suspected or confirmed pulmonary hypertension/pulmonary hypertensive vascular disease. Expert consensus

- statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Pediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. *Heart* 2016;102:ii30–5.
- [43] Moledina S, Pandya B, Barsota M, et al. Prognostic significant of cardiac magnetic resonance imaging in children with pulmonary hypertension. *Circ: CV Imag* 2013;6:407–14.
- [44] Pereira KD, Webb BD, Blakely ML, Cox Jr. CS, Lally KP. Sequelae of recurrent laryngeal nerve injury after patent ductus arteriosus ligation. *Int J Pediatr Otorhinolaryngol* 2006;70:1609–12.
- [45] Clement WA, El-Hakim H, Phillipos EZ, Cote JJ. Unilateral vocal cord paralysis following patent ductus arteriosus ligation in extremely low-birth-weight infants. *Arch Otolaryngol Head Neck Surg* 2008;134(1):28–33.
- [46] Mourani PM, Ivy DD, Gao D, Abman SH. Pulmonary vascular effects of inhaled nitric oxide and oxygen tension in bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2004 Nov 1;170(9):1006–13.
- [47] Lakshminrusimha S, Mathew B, Leach CL. Pharmacologic strategies in neonatal pulmonary hypertension other than nitric oxide. *Semin Perinatol* 2016;40:160–73.
- [48] Lagatta JM, Hysinger EB, Zaniletti I, et al. The impact of pulmonary hypertension in preterm infants with severe bronchopulmonary dysplasia through 1 year. *J Pediatr* 2018;203:218–24.
- [49] Berkelhamer SK, Mestan KK, Steinhorn R. An update on the diagnosis and management of bronchopulmonary dysplasia (BPD)-associated pulmonary hypertension. *Semin Perinatol* 2018;42:432–43.
- [50] Drossner DM, Kim DW, Maher KO, Mahle WT. Pulmonary vein stenosis: prematurity and associated conditions. *Pediatrics* 2008;122:e656–61.
- [51] Swier NL, Richards B, Cua CL, Lynch SK, Yin H, Nelin LD, Smith CV, Backes CH. Pulmonary vein stenosis in neonates with severe bronchopulmonary dysplasia. *Am J Perinatol* 2016;33:671–7.
- [52] Mahgoub L, Kaddoura T, Kameny AR, et al. Pulmonary vein stenosis of ex-premature infants with pulmonary hypertension and bronchopulmonary dysplasia, epidemiology, and survival from a multicenter cohort. *Pediatr Pulmonol* 2017 Aug;52(8):1063–70.
- [53] Callahan R, Kieren MW, Baird CW, et al. Adjunct targeted biologic inhibition agents to treat aggressive multivessel intraluminal pediatric pulmonary vein stenosis. *J Pediatr* 2018 Jul;198:29–35.e5.
- [54] Starr MC, Flynn JT. Neonatal hypertension: cases, causes, and clinical approach. *Pediatr Nephrol* 2019;34:787–99.
- [55] Abman SH, Warady BA, Lunn GM, Koops BL. Systemic hypertension in infants with bronchopulmonary dysplasia. *J Peds* 1984;104(6):928–31.
- [56] Anderson AH, Warady BA, Daily DK, Johnson JA, Thomas MK. Systemic hypertension in infants with severe bronchopulmonary dysplasia: associated clinical factors. *Amer J Peri* 1993;10(3):190–3.
- [57] Jenkins RD, Aziz JK, Giervers LL, Mooers HM, Fino N, Rozansky DJ. Characteristics of hypertension in premature infants with and without chronic lung disease: a long-term multi-center study. *Pediatr Nephrol* 2017;32:2115–24.
- [58] Chappell, et al. Pulmonary clearance of norepinephrine in lambs. *Pediatr Res* 1991;29(1):93–7.
- [59] Mills NL, Miller JJ, Anand A, et al. Increased arterial stiffness in patients with chronic obstructive pulmonary disease: a mechanism for increased cardiovascular risk. *Thorax* 2008;63:306–11.
- [60] Sehgal A, Malikiwi A, Paul E, Tan K, Menahem S. Systemic arterial stiffness in infants with bronchopulmonary dysplasia: potential cause of systemic hypertension. *J Perinatol* 2016:564–9.
- [61] Palmiero P, et al. Left ventricular diastolic function in hypertension: methodological considerations and clinical implications. *J Clin Med Res* 2015;7(3):137–44.
- [62] Peterson AL, Frommelt PC, Mussatto K. Presentation and echocardiographic markers of neonatal hypertensive cardiomyopathy. *Pediatrics* 2006;118(3):e782–5.
- [63] Dionne JM, Flynn JT. Hypertension in the neonate. *NeoReviews* 2012;13:e401–9.
- [64] Blowey DL, Duda PJ, Stokes P, Hall M. Incidence and treatment of hypertension in the neonatal intensive care unit. *J Am Soc Hypertens* 2011;5(6):478–83.
- [65] Ghandi Y, Habibi D, Nasri K, Alinejad S, et al. Effect of well-controlled gestational diabetes on left ventricular diastolic dysfunction in neonates. *J Matern Fetal Neonatal Med* 2019 Jul;32(13):2101–6.
- [66] Kozak-Barany A, Jokinen E, Saraste M, Tuominen J, Valimaki I. Development of left ventricular systolic and diastolic function in preterm infants during the first month of life: a prospective followup study. *J Peds* 2001;139:539–45.
- [67] Wong IH, Digby AM, et al. Dexamethasone given to premature infants and cardiac diastolic function in early childhood. *J Peds* 2011;159:227–31.
- [68] Mourani PM, Ivy DD, et al. Left ventricular diastolic dysfunction in bronchopulmonary dysplasia. *J Peds* 2008;152(2):291–3.
- [69] Mourani PM, Abman SH. Pulmonary hypertension and vascular abnormalities in bronchopulmonary dysplasia. *Clin Perinatol* 2015;42(4):839–55.
- [70] Baker CD, Alvira CM. Disrupted lung development and bronchopulmonary dysplasia: opportunities for lung repair and regeneration. *Curr Opin Pediatr* 2014 Jun;26(3):306–14.